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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
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3-Furanyl analogs of toxoflavine as kinase inhibitors

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3-FURANYL ANALOGS OF TOXOFLAVINE AS KINASE INHIBITORS.

This invention relates to 1H-pyrimido[5.4-e][1,2,4]triazine-5,7-dione derivatives that inhibit cyclin-dependent serine/threonine kinases (Cdks), as well as kinases and phosphatases involved in cell cycle regulation such as the tyrosine kinases Wee1, Mik1 and Myt1 or the tyrosine dephosphatases such as Cdc25 and Pyp3. Cyclin-dependent kinases belong to the main regulators of cell division in eukaryotic organisms and their deregulation results in rearrangements, amplification and loss of chromosomes, events that are causally associated with cancer. As such these compounds are useful to treat cell proliferative disorders such as atherosclerosis, restenosis and cancer.

Cell cycle kinases are naturally occurring enzymes involved in regulation of the cell cycle (Meijer L., "Chemical Inhibitors of Cyclin-Dependent Kinases", *Progress in Cell Cycle Research*, 1995; 1:35 1-363). Typical enzymes include serine/threonine kinases such as the cyclin-dependent kinases (cdk) cdk1, cdk2, cdk4, cdk5, cdk6 as well as tyrosine kinases such as AKT3 or Wee 1 kinase and tyrosine phosphatases such as cdc25 involved in cell cycle regulation. Increased activity or temporally abnormal activation or regulation of these kinases has been shown to result in development of human tumors and other proliferative disorders. Compounds that inhibit cdks, either by blocking the interaction between a cyclin and its kinase partner, or by binding to and inactivating the kinase, cause inhibition of cell proliferation, and are thus useful for treating tumors or other abnormally proliferating cells.

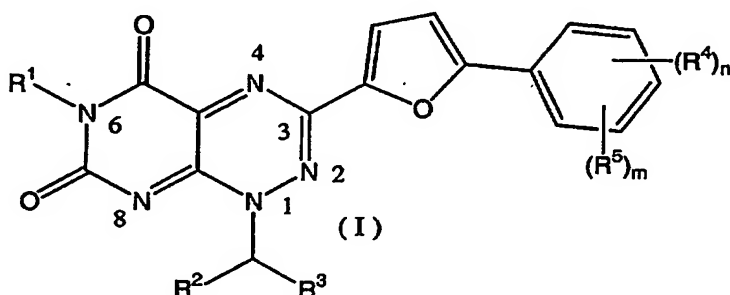
Several compounds that inhibit cdks have demonstrated preclinical anti-tumor activity. For example, flavopiridol is a flavonoid that has been shown to be a potent inhibitor of several types of breast and lung cancer cells (Kaur, et al., *J. Natl. Cancer Inst.*, 1992;84:1736-1740; *Int. J. Oncol.*, 1996;9:1143-1168). The compound has been shown to inhibit cdk2 and cdk4. Olomoucine [2-(hydroxyethylamino)-6-benzylamine-9-methylpurine] is a potent inhibitor of cdk2 and cdk5 (Vesely, et al., *Eur. J. Biochem.*, 1994;224:77 1-786), and has been shown to inhibit proliferation of approximately 60 different human tumor cell lines used by the National Cancer Institute (NCI) to screen for new cancer therapies (Abraham, et al., *Biology of the Cell*, 1995;83: 105-120). More recently, flavonoid derivatives such toxoflavine (*J.Chem.Soc.Perkin Trans. 1*, 2001, 130-137) and 7-azapteridine derivatives (Japanese Unexamined Patent Application Laid Open H9-255681) have been disclosed as antineoplastic agents.

The toxoflavine derivatives of the present invention differ thereof in that the substituent at position 3 is furanyl which is further substituted with water solubility enhancing functionalities

such as alcohol groups, aliphatic basic amine entities and aminosulphon(amine) substituents or a combination thereof, without loss of biological activity as anti-proliferative compounds.

Accordingly, the underlying problem to be solved by the present invention was to find further
5 toxoflavine derivatives with an improved water solubility and concomitant cellular activity.

This invention concerns compounds of formula (I)



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

m represents an integer being 0 or 1;

15 *n* represents an integer being 0, 1 or 2;

*R*¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with phenyl, pyridinyl or morpholinyl, phenyl, phenyl substituted with one or where possible more substituents being selected from C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, -NO₂ or cyano-C₁₋₄alkyl, piperidinyl or piperidinyl substituted with C₁₋₄alkyl, phenyl-C₁₋₄alkyl or C₁₋₄alkyloxycarbonyl;

20 *R*² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl or hydroxy;

*R*³ represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl or hydroxy; or

*R*² and *R*³ taken together with the carbon atom to which they are attached form a

C₃₋₈cycloalkyl or Het¹ wherein said C₃₋₈cycloalkyl or Het¹ each independently may

optionally be substituted with one, or where possible, two or three substituents each

25 independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl

C₁₋₄alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or -C(=NH)-NH₂;

*R*⁴ represents halo, hydroxy or C₁₋₄alkyloxy;

*R*⁵ represents formyl, C₁₋₄alkyl, C₁₋₄alkyloxy, Het², -NO₂, -SO₂-Het⁶, aminosulfonyl, -SO₂-

NR¹²R¹³, C₁₋₄alkyl substituted with one or where possible more substituent being selected

30 from hydroxy, halo, Het³, NR⁶R⁷ or formyl, C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴, NR⁸R⁹ or -C(=O)-Het⁴;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁵, aminosulphonyl, mono- or di(C₁₋₄alkyl)sulfonyl, C₁₋₄alkylsulfonyl, C₁₋₄alkyloxyC₁₋₄alkyl, methoxyC₁₋₄alkyl or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, Het⁵, C₁₋₄alkyloxycarbonyl or C₁₋₄alkylsulfonyl;

5 R⁸ and R⁹ are each independently selected from hydrogen, mono- or di(C₁₋₄alkyl)aminosulphonyl or aminosulphonyl;

R¹² and R¹³ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl;

Het¹ represents piperidinyl;

10 Het² represents a heterocycle selected from piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl;

15 Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, NR¹⁰R¹¹, imidazolyl, tetrahydropyrimidinyl, amino, NH₂-SO₂-O-, mono- or di(C₁₋₄alkyl)amino- SO₂-O-, NH₂-SO₂-NH-,
20 mono- or di(C₁₋₄alkyl)amino- SO₂-NH-, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

R¹⁰ and R¹¹ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

25 Het⁴ represents a heterocycle selected from morpholinyl, piperidinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulphonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or C₁₋₄alkyl substituted with one or more hydroxy;

30 Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl, or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁶ represents morpholinyl.

35 As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-

methylpropyl, 2,2-dimethylethyl and the like; C₃₋₈cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl and cyclo-octanyl; C₁₋₄alkyloxy defines straight or branched saturated hydrocarbon radicals such as methoxy, ethoxy, propyloxy, butyloxy, 1-methylethyloxy, 2-methylpropyloxy and the like.

5

As used herein before, the term (=O) forms a carbonyl moiety with the carbon atom to which it is attached. The term (=NH) forms a imino moiety with the carbon atom to which it is attached. The term formyl as used herein before refers to a radical of formula -CH(=O).

- 10 The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the
- 15 like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

- 20 The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic base addition salt forms which the compounds of formula (I) are able to form. Examples of such base addition salt forms are, for example, the sodium, potassium, calcium salts, and also the salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, *N*-methyl-D-glucamine,
- 25 hydrabamine, amino acids, e.g. arginine, lysine.

Conversely said salt forms can be converted by treatment with an appropriate base or acid into the free acid or base form.

- 30 The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

- The term stereochemically isomeric forms as used hereinbefore defines the possible different
- 35 isomeric as well as conformational forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically and conformationally isomeric forms, said mixtures

containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

5

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein the azapteridine-nitrogen is *N*-oxidized.

10

A preferred group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

R^1 represents C_{1-4} alkyl preferably methyl, piperidinyl or piperidinyl substituted with phenyl- C_{1-4} alkyl or C_{1-4} alkyloxycarbonyl;

R^2 represents hydrogen, phenyl, C_{1-4} alkyl or C_{1-4} alkyl substituted with phenyl;

15

R^2 represents hydrogen, phenyl, C_{1-4} alkyl or C_{1-4} alkyl substituted with phenyl; or

R^2 and R^3 taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C_{1-4} alkyloxycarbonyl, C_{1-4} alkylsulfonyl, aminosulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl or phenylcarbonyl;

20

R^4 represents halo, preferably Cl or R^4 represents C_{1-4} alkyloxy;

R^5 represents formyl, $-SO_2$ -Het⁶, C_{1-4} alkyl substituted with one or where possible more substituent being selected from hydroxy, Het³, NR^6R^7 or formyl, or R^5 represents C_{1-4} alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or $-C(=O)$ -Het⁴;

25

R^6 and R^7 are each independently selected from hydrogen, C_{1-4} alkyl, Het⁵, C_{1-4} alkylsulfonyl, C_{1-4} alkyloxy C_{1-4} alkyl, or C_{1-4} alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, hydroxy C_{1-4} alkyl, aminosulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl, $NR^{10}R^{11}$, imidazolyl, tetrahydropyrimidinyl, amino, mono- or di(C_{1-4} alkyl)amino- SO_2 -NH-, hydroxy C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl or C_{1-4} alkyloxy;

35

R^{10} and R^{11} are each independently selected from hydrogen or C_{1-4} alkyl;

Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

5 Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

10 A group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

R¹ represents C₁₋₄alkyl preferably methyl, C₁₋₄alkyl substituted with pyridinyl, phenyl, piperidinyl or piperidinyl substituted with C₁₋₄alkyloxycarbonyl;

R² represents hydrogen or C₁₋₄alkyl preferably methyl;

15 R³ represents hydrogen or C₁₋₄alkyl preferably methyl; or

R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl or -C(=NH)-NH₂;

20 R⁴ represents halo or C₁₋₄alkyloxy;

R⁵ represents Het², C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, halo, Het³ or NR⁶R⁷, or R⁵ represents C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

25 R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het² represents piperazinyl;

30 Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl preferably methyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

35 Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

5

A further group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

R¹ represents C₁₋₄alkyl, piperidinyl, or piperidinyl substituted with C₁₋₄alkyloxycarbonyl preferably t-butyloxycarbonyl;

10 R² represents C₁₋₄alkyl preferably methyl;

R³ represents C₁₋₄alkyl preferably methyl; or

R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl or -C(=NH)-NH₂;

15

R⁴ represents halo or C₁₋₄alkyloxy;

R⁵ represents Het², C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, Het³ or NR⁶R⁷, or R⁵ represents C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

20

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het² represents piperazinyl;

25

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl preferably methyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

30

Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

35

Also of interest, are the group of compounds of formula (I) wherein one or more of the following restrictions apply :

R¹ represents C₁₋₄alkyl preferably methyl

R² represents hydrogen, C₁₋₄alkyl or phenyl;

5 R³ represents hydrogen, C₁₋₄alkyl or phenyl; or

R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl preferably t-butyloxycarbonyl or aminosulfonyl;

10 R⁴ represents halo, preferably Cl or Br or R⁴ represents C₁₋₄alkyloxy preferably methoxy;

R⁵ represents C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, Het³ or NR⁶R⁷, or R⁵ represents C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

15 R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁵, C₁₋₄alkylsulfonyl, C₁₋₄alkyloxyC₁₋₄alkyl, or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het³ represents a heterocycle selected from morpholinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, aminosulfonyl, NR¹⁰R¹¹, imidazolyl, amino, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

20 R¹⁰ and R¹¹ are each independently selected from hydrogen or C₁₋₄alkyl;

Het⁴ represents morpholinyl;

25 Het⁵ represents a heterocycle selected from pyridinyl, or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

30 A remarkable group of compounds are those according to formula (I) wherein one or more of the following restrictions apply;

n represents an integer being 0, 1 or 2;

35 R¹ represents C₁₋₄alkyl, preferably methyl or R¹ represents phenyl, phenyl substituted with C₁₋₄alkyloxycarbonyl or -NO₂, or R¹ represents C₁₋₄alkyl substituted with pyridinyl or morpholinyl;

R² represents hydrogen, or C₁₋₄alkyl preferably methyl;

R³ represents hydrogen, phenyl or C₁₋₄alkyl preferably methyl;

R⁴ represents halo preferably Cl;

R⁵ represents C₁₋₄alkyl substituted with one or where possible more halo substituents preferably said halo substituted C₁₋₄alkyl being trifluoromethyl.

5 It is also an embodiment of the present invention to provide a group of compounds of formula (I) wherein one or more of the following restrictions apply;

R¹ represents C₁₋₄alkyl preferably methyl, C₁₋₄alkyl substituted with phenyl, or R¹ represents piperidinyl or piperidinyl substituted with C₁₋₄alkyloxycarbonyl;

R² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl;

10 R² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl; or

R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, C₁₋₄alkylsulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or phenylcarbonyl;

15 R⁴ represents halo, preferably Cl or R⁴ represents C₁₋₄alkyloxy preferably methoxy;

R⁵ represents formyl, C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, Het³ or NR⁶R⁷, or R⁵ represents C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

20 R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁵, C₁₋₄alkylsulfonyl, methoxyC₁₋₄alkyl, or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het² represents piperidinyl optionally substituted with C₁₋₄alkyloxycarbonyl;

25 Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, NR¹⁰R¹¹, imidazolyl, tetrahydropyrimidinyl, amino, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

30 R¹⁰ and R¹¹ are each independently selected from hydrogen or C₁₋₄alkyl;

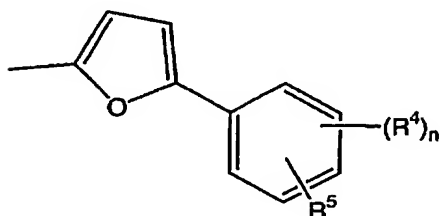
Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

35 Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

Other special group of compounds are;

- those compounds of formula (I) wherein R^1 is methyl;
- those compounds of formula (I) wherein R^2 and R^3 taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl, preferably cyclopentyl;
- those compounds of formula (I) wherein R^2 and R^3 each represents a C_{1-4} alkyl, preferably methyl;
- those compounds of formula (I) wherein Het^3 represent a heterocycle selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with one C_{1-4} alkyl substituent, preferably methyl, more preferably with the methyl in the para position relative to the carbon atom bearing the R^5 substituent.
- those compounds of formula (I) with R^5 being a C_{1-4} alkyloxy said C_{1-4} alkyloxy being substituted with either;
 - o one Het^4 substituent with Het^4 being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with one C_{1-4} alkyl substituent, preferably methyl, more preferably with the methyl in the para position relative to the carbon atom bearing the R^5 substituent, or
 - o one $-C(=O)-Het^4$ substituent with Het^4 being piperazinyl preferably substituted with C_{1-4} alkyl, more preferably substituted with methyl.
- those compounds of formula (I) wherein R^6 or R^7 each represent Het^5 with said Het^5 being selected from the group consisting of piperidinyl, piperidinyl substituted with aminosulfonyl or mono- or di(C_{1-4} alkyl)aminosulfonyl, preferably dimethylaminosulfonyl, and pyrrolidinyl optionally substituted C_{1-4} alkyloxycarbonyl, preferably ethoxycarbonyl.
- those compounds of formula (I) wherein R^6 or R^7 represent C_{1-4} alkyl substituted with Het^5 said Het^5 being selected from pyridinyl.
- those compounds of formula (I) wherein m represents 0 and R^4 represents halo, preferably chloro.

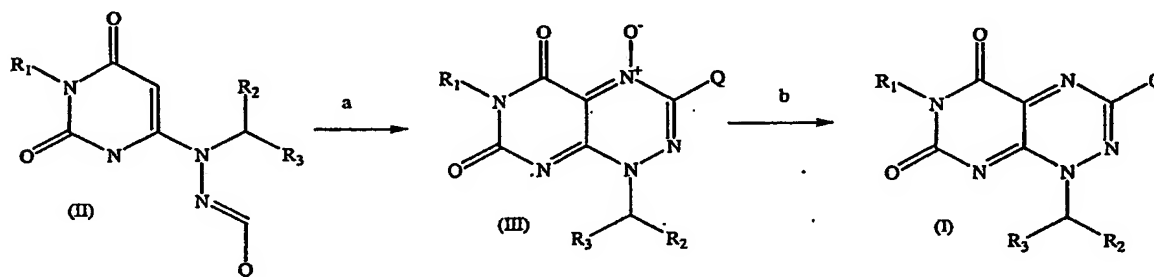
In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol Q.

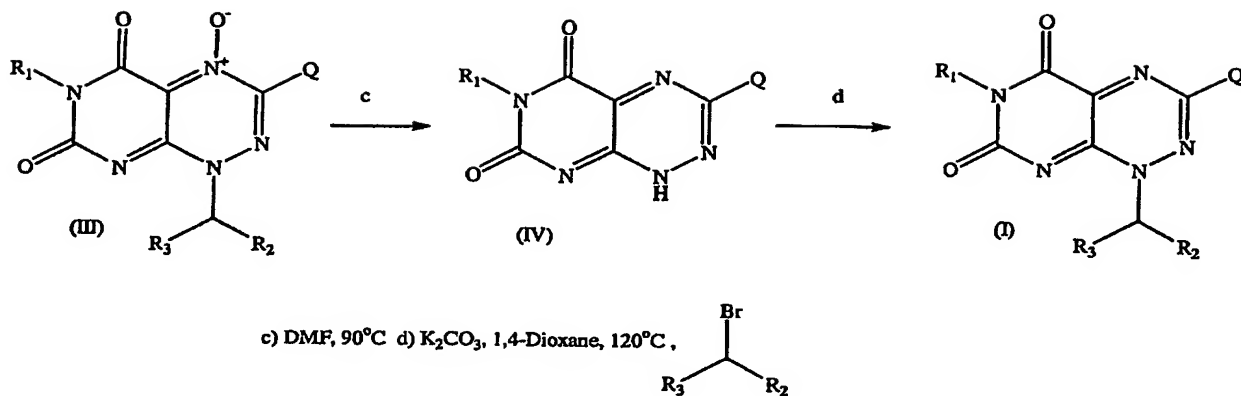
The compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry and described for instance in the following references; "Heterocyclic Compounds" – Vol.24 (part4) p 261-304 Fused pyrimidines, Wiley – Interscience ; Chem. Pharm. Bull., Vol 41(2) 362-368 (1993);
 5 J.Chem.Soc., Perkin Trans. 1, 2001, 130-137.

As further exemplified in the experimental part of the description, the compounds of formula (I) were generally prepared using three alternative synthesis schemes. In a first alternative, the compounds of formula (I) were prepared by nitrosative cyclisation of intermediates of formula (II) with NaNO₂ in acetic acid (AcOH). The thus obtained azapteridines comprising the 5-nitroso intermediates of formula (III) are subsequently converted in the final compounds with formula (I) by refluxing the mixture in for example acetic anhydride or ethanol (EtOH) comprising dithiothreitol (DTT).
 10

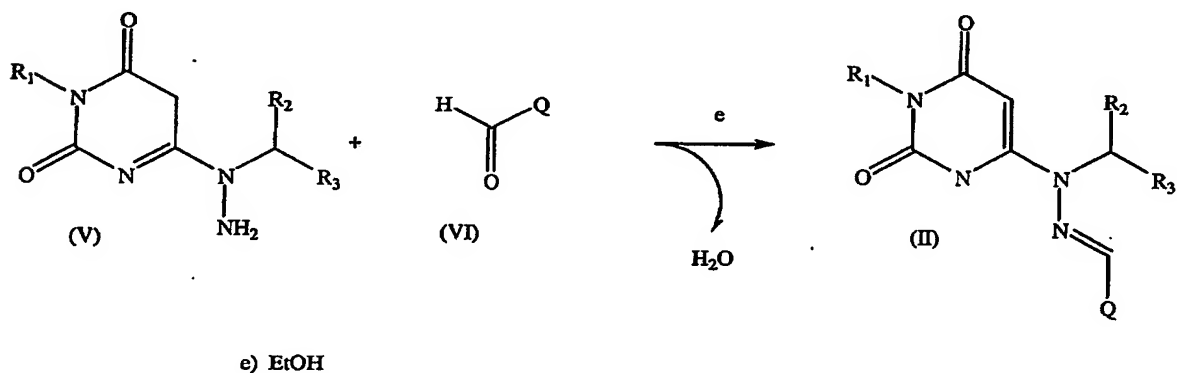


15 a) NaNO₂, AcOH, H₂O b) DTT, EtOH

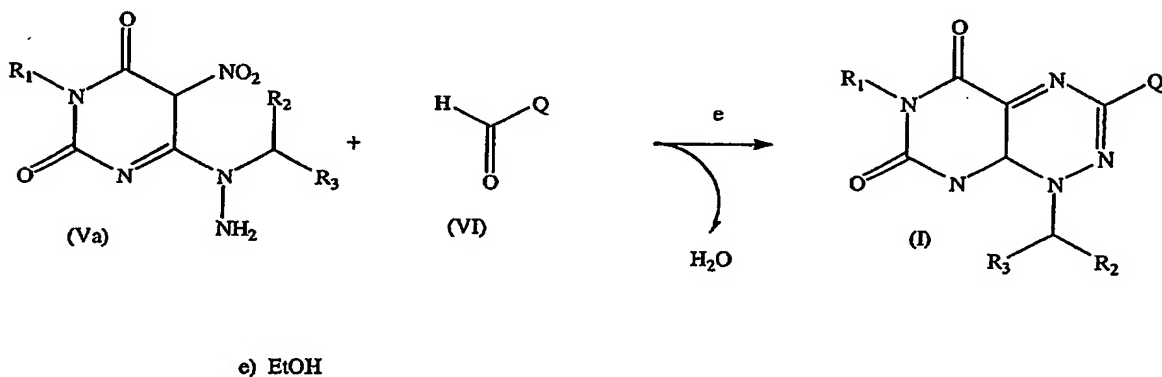
Alternatively, the intermediates of formula (III) are dealkylated by heating in N,N-Dimethylformamide (DMF) at temperatures ranging from 90-150°C for 3-6 hours. The thus obtained reumycin derivatives of formula (IV) are subsequently alkylated in 1,4-dioxane further comprising an appropriate base such as anhydrous potassium carbonate, sodium hydride or sodium hydrogen carbonate, preferably anhydrous potassium carbonate and an alkylating agent such as dialkylsulfate, alkyl iodide or alkyl bromide, preferably alkyl bromide, yielding the final compounds of formula (I).
 20



In the aforementioned reaction schemes, the substituted imines or Schiffs bases of formula (II) can generally be prepared by reacting a primary amine of formula (V) with an aldehyde of formula (VI) in a traditional condensation reaction using amongst others ethanol as a suitable solvent.

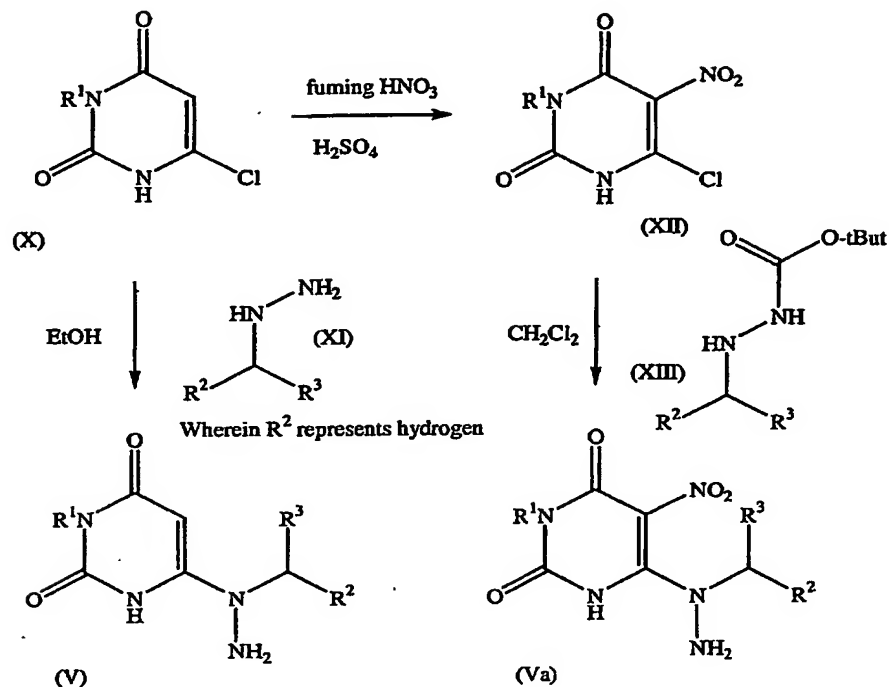


10 Finally, as an alternative to the above, the compounds of formula (I) can be prepared in a condensation reaction between a primary amine of formula (Va) with an aldehyde of formula (VI) using amongst others, ethanol as a suitable solvent.



The intermediates of formula (V) and (Va) were generally prepared as depicted in reaction scheme 1.

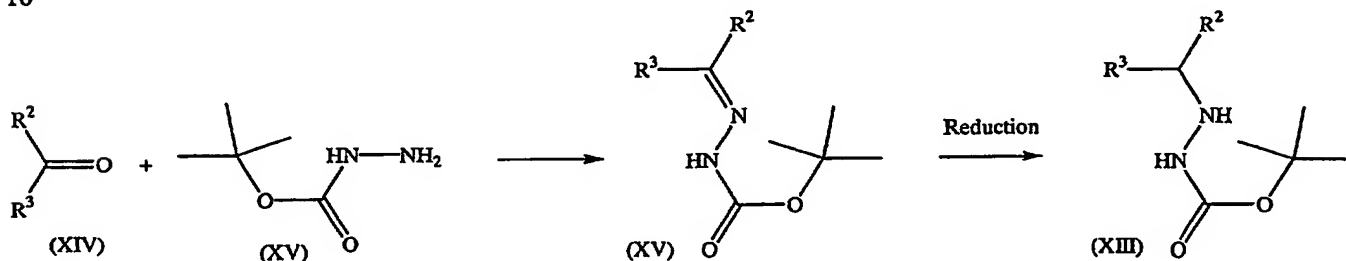
Scheme 1



5

In order to introduce further R^2 substituents the urea derivative of formula (XI) was shielded with the protective group t -butoxycarbonyl. This is introduced by treating a ketone of formula (XIV) with t -butoxycarbonylhydrazine and subsequent reduction with $Pt/C/H_2$ in $EtOH$ or by the slow addition of $NaBH_4$ in THF.

10



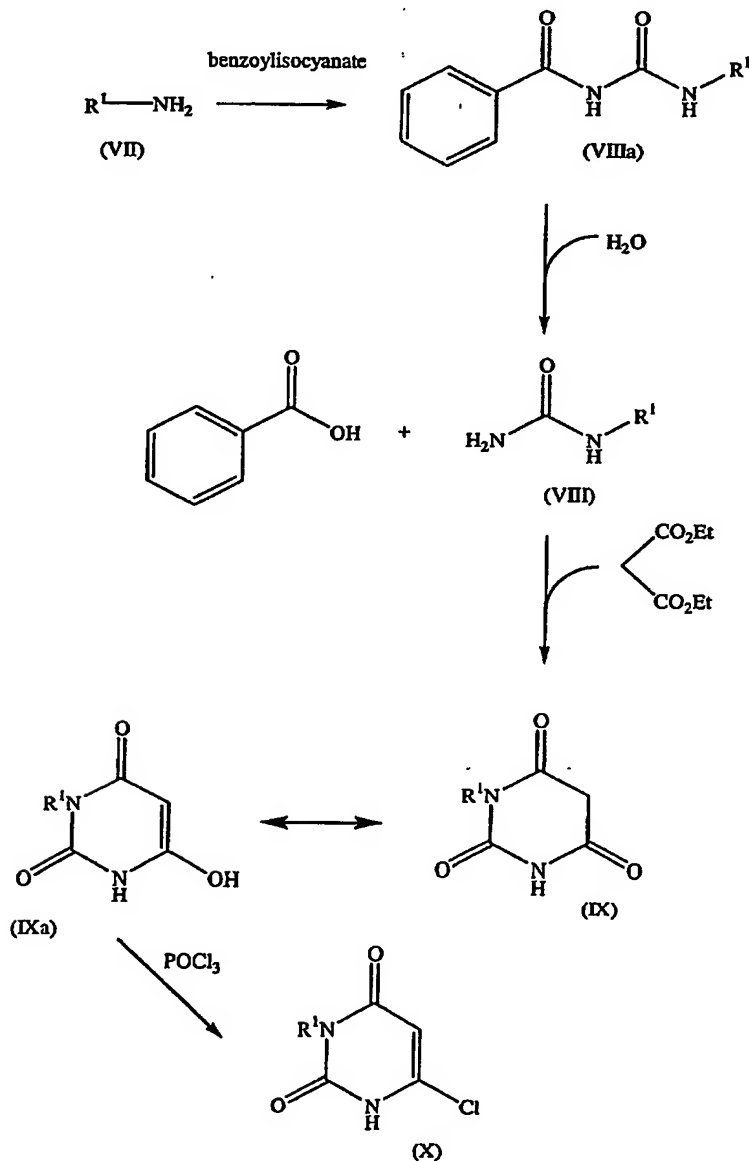
The protecting group is easily removed by treating the protected amine with trifluoroacetic acid (TFA) in CH_2Cl_2 as a solvent.

15

As depicted in scheme 2, art known techniques such as described in "Introduction to Organic Chemistry" – A. Streitweiser, second ed. Macmillan Publishing Inc. p 1104, were used to prepare the pyrimidines of formula (IX). In general, the synthesis of said pyrimidines consists of a condensation between 1,3-dicarbonyl compounds such as diethylpropanedioate and a material containing the general structure N-C-N such as urea and the compounds of formula (VIII). The urea compounds of formula (VIII) are prepared using art know techniques, in particular the reaction of isocyanates such as benzoylisocyanate with an amine such as represented by formula (VII). In this particular reaction scheme, the benzoyl substituent is released from the urea complex of formula (VIIIa) by hydration with water.

10

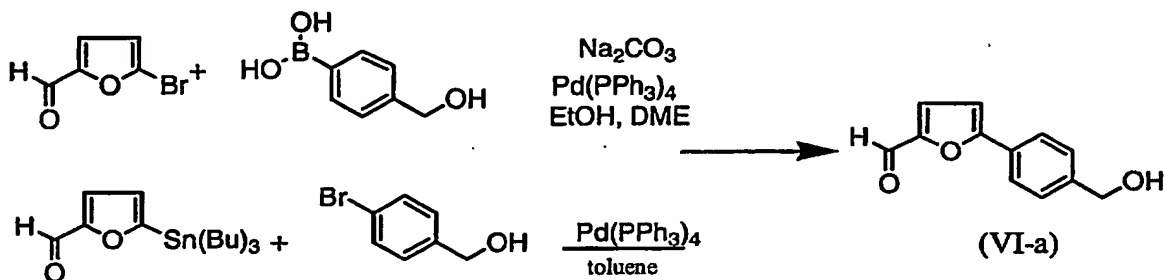
Scheme 2



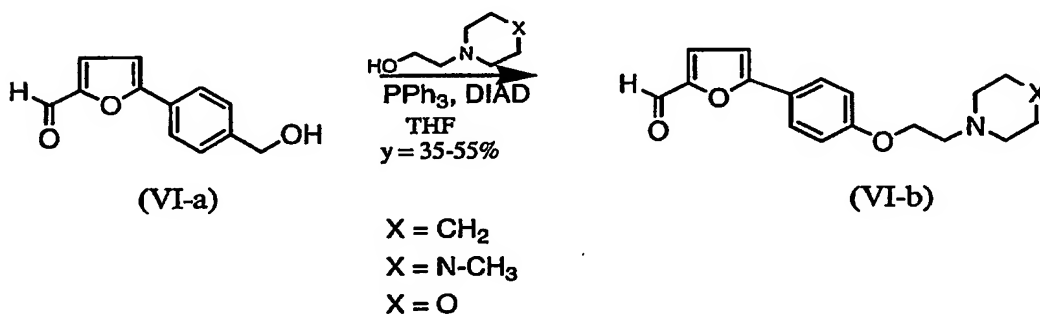
In a final step the tautomeric form of the thus obtained pyrimidines (IXa) were halogenated using an appropriate halogenating agent such as SOCl₂, POCl₃, PCl₅ or PBr₃.

The starting furanyl aldehyde of formula (VI) was prepared by the two coupling reaction described as followed:

Scheme 3



Wherein (VI-a) could be further converted using art known procedures such as the Mitsunobu reaction using the corresponding amino- alcohol. For example;



Where necessary or desired, any one or more of the following further steps in any order may be performed :

- (i) removing any remaining protecting group(s);
- (ii) converting a compound of formula (I) or a protected form thereof into a further compound of formula (I) or a protected form thereof;
- (iii) converting a compound of formula (I) or a protected form thereof into a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof;
- (iv) converting a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof into a compound of formula (I) or a protected form thereof;

- (v) converting a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof into another *N*-oxide, a pharmaceutically acceptable addition salt a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof;
- (vi) where the compound of formula (I) is obtained as a mixture of (R) and (S) enantiomers resolving the mixture to obtain the desired enantiomer.

Compounds of formula (I), *N*-oxides, addition salts, quaternary amines and stereochemical isomeric forms thereof can be converted into further compounds according to the invention using procedures known in the art, for example :

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C₍₁₋₆₎alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

Additionally, the N-atoms in compounds of formula (I) can be methylated by art-known methods using CH₃-I in a suitable solvent such as, for example 2-propanone, tetrahydrofuran or dimethylformamide.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation of which some examples are mentioned hereinabove.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula

(I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

The compounds of the present invention are useful because they possess pharmacological properties. They can therefore be used as medicines.

5 As described in the experimental part hereinafter, the growth inhibitory effect and anti-tumor activity of the present compounds has been demonstrated in vitro, in enzymatic assays on kinases and phosphatases involved in cell cycle regulation. Anti-tumor activity was also demonstrated in vitro, in a cell based assay comprising contacting the cells with the compounds and assessing the effect of AKT3 on MAPK phosphorylation. In an alternative assay, the
10 growth inhibitory effect of the compounds was tested on the ovarian carcinoma cell line A2780 using art known cytotoxicity assays such as LIVE/DEAD (Molecular Probes) or MTT.

Accordingly, the present invention provides the compounds of formula (I) and their pharmaceutically acceptable *N*-oxides, addition salts, quaternary amines and stereochemically
15 isomeric forms for use in therapy. More particular in the treatment or prevention of cell proliferation mediated diseases. The compounds of formula (I) and their pharmaceutically acceptable *N*-oxides, addition salts, quaternary amines and the stereochemically isomeric forms may hereinafter be referred to as compounds according to the invention.

20 Disorders for which the compounds according to the invention are particularly useful are atherosclerosis, restinosis and cancer.

In view of the utility of the compounds according to the invention, there is provided a method for the treatment of an animal, for example, a mammal including humans, suffering from a cell
25 proliferative disorder such as atherosclerosis, restinosis and cancer, which comprises administering an effective amount of a compound according to the present invention.

Said method comprising the systemic or topical administration of an effective amount of a compound according to the invention, to warm-blooded animals, including humans.

30

In yet a further aspect, the present invention provides the use of the compounds according to the invention in the manufacture of a medicament for treating any of the aforementioned cell proliferative disorders or indications.

35 The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutical effect will be, of course, vary with the particular compound, the route of administration, the age and condition of the

recipient, and the particular disorder or disease being treated. A suitable daily dose would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day.

5

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention further provides a pharmaceutical composition comprising a compound according to the present invention, together with a pharmaceutically acceptable carrier or diluent. The carrier or diluent must be

10 "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

15

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8 : Pharmaceutical preparations and their Manufacture). A therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for

20 administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous, or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water,

25 glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For

30 parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the

35 compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant

deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α -, β - or γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with $C_{(1-6)}$ alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxy $C_{(1-6)}$ alkyl, particularly hydroxyethyl, hydroxy-propyl or hydroxybutyl; carboxy $C_{(1-6)}$ alkyl, particularly carboxymethyl or carboxy-ethyl; $C_{(1-6)}$ alkylcarbonyl, particularly acetyl; $C_{(1-6)}$ alkyloxycarbonyl $C_{(1-6)}$ alkyl or carboxy- $C_{(1-6)}$ alkyloxy $C_{(1-6)}$ alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; $C_{(1-6)}$ alkylcarbonyloxy $C_{(1-6)}$ alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD,

2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD (2-HP- β -CD).

5 The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

10 The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

15 The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

Experimental part

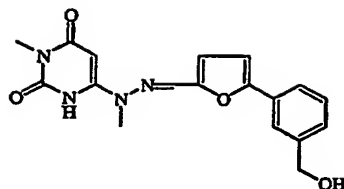
20 Hereinafter, the term 'RT' means room temperature, 'THF' means tetrahydrofuran, 'AcOH' means Acetic Acid, 'EtOH' means ethanol, DME means dimethyl ether, DIPE means diisopropyl ether, TFA means trifluoroacetic acid.

A. Preparation of the intermediates

25 Example A1

a) A solution of 5-Bromo-2-furancarboxaldehyde (0.0171 mol) in DME (65ml) was added dropwise to a solution of Pd(PPh₃)₄ (0.00007 mol) in DME (50ml) at room temperature under N₂. The mixture was stirred for 15 minutes. A solution of (3-hydroxyphenyl)boronic acid (0.0257 mol) in EtOH (18ml) was added. The mixture was stirred for 15 minutes. 2M K₂CO₃ (75ml) was added. The mixture was stirred and refluxed for 4 hours, cooled to room temperature, concentrated and taken up by CH₂Cl₂. The organic layer was washed by H₂O, dried over MgSO₄, filtered and evaporated. The residue (5.9g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. Yielding: 3g of intermediate 1 (88%).

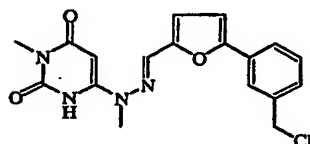
c) Preparation of



(intermediate 2)

A mixture of intermediate 1 (0.0046 mol) and 3-methyl-6-(1-methylhydrazino)-2,4(1H,3H)-Pyrimidinedione (0.0046 mol) in EtOH (20ml) was stirred at 60°C for 3 hours, cooled to room temperature. A precipitate was filtered off, washed with diethyl ether then EtOH and dried. Yielding: 1g of intermediate 2 (60%).

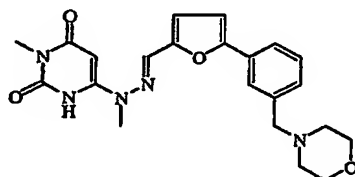
d) Preparation of



(intermediate 3)

SOCI₂ (0.0485 mol) was added dropwise at 5°C to a mixture of intermediate 2 (0.0121 mol) in CH₂Cl₂ (80ml). The mixture was brought to room temperature, then stirred for 8 hours and the solvent was evaporated till dryness. Yielding: 6.2g intermediate 3 (>100%). This product was used directly in the next reaction step.

e) Preparation of

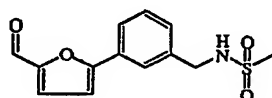


(intermediate 4)

A mixture of intermediate 3 (0.0121 mol) and morpholine (0.0242 mol) in CH₃CN (110ml) was stirred and refluxed for 4 hours, then brought to room temperature. The precipitate was filtered, washed with H₂O, then washed twice with EtOH, then washed with diethyl ether and dried. The residue (4.5g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂ 100 to CH₂Cl₂/CH₃OH 98/2; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 3.2g intermediate 4 (62%).

Example A2

a) Preparation of



(intermediate 5)

A mixture of 5-(Tributylstannyl)furan-2-carbaldehyde (0.032 mol), N-(3-Bromobenzoyl)methanesulfonamide (0.016 mol) and Pd(PPh₃)₄ (0.0016 mol) in toluene (120ml) was stirred and refluxed for 5 hours, then brought to room temperature. The mixture was filtered. The filtrate was evaporated. The residue (16g) was purified by column

CN1C(=O)C=C(N1)N(N)C=Nc2ccoc2-c3ccc(cc3)CCNS(=O)(=O)C

A mixture of 3-methyl-6-(1-methylhydrazino)-2,4(1H,3H)-Pyrimidinedione (0.0059 mol) and intermediate 5 (0.0057 mol) in EtOH (15ml) was stirred and refluxed for 3 hours, then brought to room temperature. The mixture was filtered. The filtrate was evaporated. Yielding: intermediate 6 (48%).

CN1C=NC(=O)NC1=CN(C)N=N/C=C/c2ccoc2S(=O)(=O)N3CCOCC3

(intermediate 7)

A mixture of 3-methyl-6-(1-methylhydrazino)- 2,4(1H,3H)-Pyrimidinedione (0.0077 mol) and 4-[(5-formyl-2-furanyl)sulfonyl]-morpholine (0.01 mol) in EtOH (15ml) was stirred and refluxed for 3 hours then brought to room temperature. The precipitate was filtered, rinsed with EtOH and dried. Yielding: intermediate 7 (58%).brought to room temperature. The precipitate was filtered, rinsed with EtOH and dried. Yielding: intermediate 7 (58%).

CN1C=NC2=C1C(=O)N(C)C2=NC=N/C=C/c3ccoc3-c4ccc(cc4)S(=O)(=O)N5CCOCC5

(intermediate 8)

A mixture of [[4-(5-formyl-2-furanyl)phenyl]sulfonyl]-morpholine (0.0105 mol), and methyl-6-(1-methylhydrazino)- 2,4(1H,3H)-Pyrimidinedione (0.0105 mol) in EtOH (70 ml) was stirred and refluxed for 2 hours then brought to room temperature. The precipitate was filtered, washed with EtOH and dried with diethyl ether. Yielding: intermediate 8 (92%).

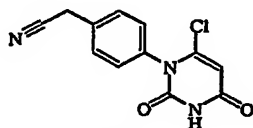
N#CCCC1=CC=C(C=C1)N2C(=O)CC(=O)NC2=O

(intermediate 11)

A mixture of N-[4-(cyanomethyl)phenyl]urea (intermediate 10) (0.1141 mol), diethyl ester propanedioic acid (0.1141 mol) and EtONa/EtOH 21% (0.1198 mol) in EtOH (250ml) was stirred and refluxed for 5 days, then brought to room temperature. The precipitate was filtered,

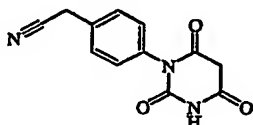
washed with EtOH, then taken up in H₂O, acidified with HCl 3N and filtered. The precipitate was washed with H₂O, then with diethyl ether and dried. Yielding: 16.5g intermediate 11 (59%).

c) Preparation of



(intermediate 12)

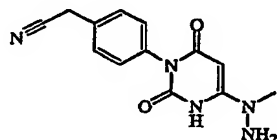
and preparation
of



(intermediate 13)

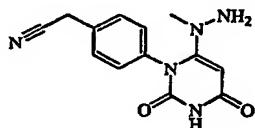
5 H₂O (0.183 mol) was added very slowly to a mixture of intermediate 11 (0.0678 mol) and POCl₃ (0.848 mol). The mixture was stirred and refluxed for 40 minutes, then brought to room temperature and the solvent was evaporated till dryness. Ice water was added very slowly. The mixture was stirred for 10 minutes. The precipitate was filtered, washed with H₂O, then with diethyl ether and dried. The residue (14.6g) was purified by column chromatography over silica
10 gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5; 15-35μm). Two fractions were collected and the solvent was evaporated. Yielding: 6.1g intermediate 12 and 0.3g intermediate 13.

d) Preparation of



(intermediate 14)

and preparation
of



(intermediate 15)

Methyl-hydrazine (0.183 mol) was added very slowly to a mixture of intermediate 12 (0.0678 mol) and intermediate 13 (0.848 mol). The mixture was stirred and refluxed for 40 minutes,
15 then brought to room temperature and the solvent was evaporated till dryness. Ice water was added very slowly. The mixture was stirred for 10 minutes. The precipitate was filtered, washed with H₂O, then with diethyl ether and dried. The residue (14.6g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5; 15-35μm). Two fractions were collected and the solvent was evaporated. Yielding: 6.1g intermediate 14 and
20 0.3g intermediate 15 .

e) Preparation of

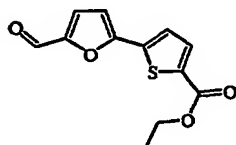
(intermediate 16)

A mixture of intermediate 14 (0.0055 mol), intermediate 15 (0.0055 mol) and 5-(3-chlorophenyl)-2-furancarboxaldehyde (0.011 mol) in EtOH (80ml) was stirred and refluxed for 1 hour and 30 minutes, then brought to room temperature. The precipitate was filtered, washed

with EtOH, then with diethyl ether and dried. The residue (4.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3; 15-40μm). Three fractions were collected and the solvent was evaporated. Yielding: intermediate 16 (20%).

5 Example A6

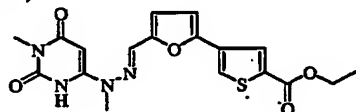
a) Preparation of



(intermediate 17)

A mixture of 5-bromo-ethyl ester 2-thiophenecarboxylic acid (0.0213 mol), 5-(tributylstannyl)-2-furancarboxaldehyde (0.0425 mol) and Pd(PPh₃)₄ (0.0021 mol) in methylphenyl (164ml) was stirred and refluxed for 3 hours. The solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 100/0 to 98/2; 15-35μm). The pure fractions were collected and the solvent was evaporated. Yielding: 3.42g intermediate 17 (64%).

b) Preparation of



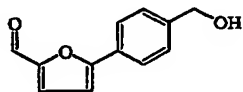
(intermediate 18)

A mixture of 3-methyl-6-(1-methylhydrazino)-2,4(1H,3H)-pyrimidinedione (0.0088 mol) and intermediate 17 (0.0088 mol) in EtOH (50ml) was stirred and refluxed for 4 hours. The precipitate was filtered off and dried. Yielding: 2.9g intermediate 18 (82%).

15

Example A7

a) Preparation of

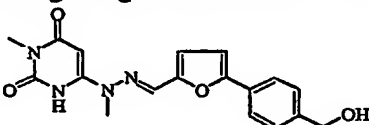


(intermediate 19)

A solution of 5-bromo-2-furancarboxaldehyde (0.0171 mol) in DME (15ml) was added dropwise at room temperature to a solution of Pd(PPh₃)₄ (0.0045 mol) in DME (50ml) under N₂ flow. The mixture was stirred for 20 minutes. A suspension of [4-(hydroxymethyl)phenyl]-boronic acid (0.0257 mol) in EtOH (18ml) was added. The mixture was stirred for 20 minutes. Na₂CO₃ (0.15 mol) was added. The mixture was stirred and refluxed for 4 hours, then brought to room temperature. The organic layer was evaporated. The residue was taken up in CH₂Cl₂ and washed with H₂O. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (4.1g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 2.8g intermediate 19 (82%).

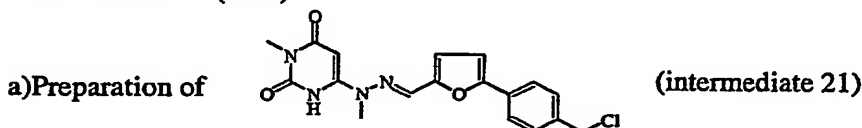
25

a) Preparation of



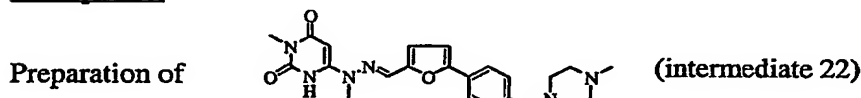
(intermediate 20)

A mixture of intermediate 19 (0.0133 mol) and 3-methyl-6-(1-methylhydrazino)-2,4(1H,3H)-pyrimidinedione (0.0133 mol) in EtOH (81ml) was stirred and refluxed for 2 hours. The precipitate was filtered, washed twice with EtOH and dried with diethyl ether. Yielding: 4.1g intermediate 20 (87%).



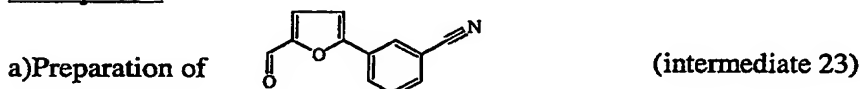
- 5 SOCl₂ (0.0349 mol) was added dropwise at 5°C to a mixture of intermediate 20 (0.0087 mol) in CH₂Cl₂ (60ml). The mixture was brought to room temperature and stirred for 4 hours and 30 minutes. The solvent was evaporated till dryness. Yielding: 3.8g intermediate 21 (>100%). This product was used directly in the next reaction step.

10 Example A8

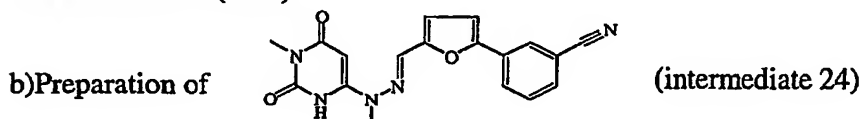


- A mixture of intermediate 21 (0.005 mol) and B (0.0101 mol) in CH₃CN (50ml) was stirred and refluxed for 3 hours, then brought to room temperature. H₂O was added. The mixture was extracted twice with EtOAc. The aqueous layer was saturated with NaCl. The organic layer was extracted with EtOAc and dried. The residue was taken up in EtOH/diethyl ether. The precipitate was filtered off and dried. Yielding: 1.2g intermediate 22 .

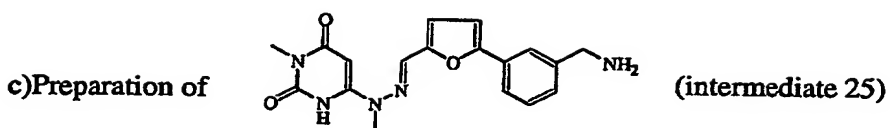
Example A9



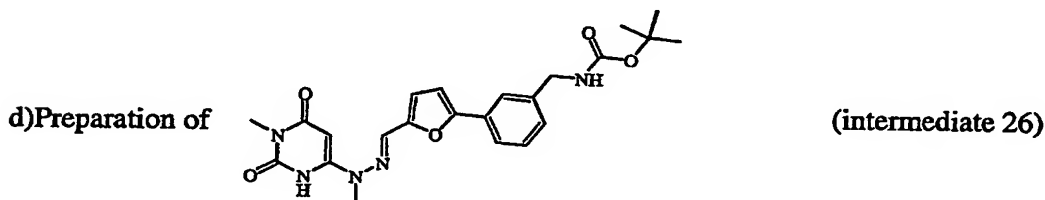
- Na₂CO₃ (83ml) then a mixture of 3-Cyanophenylboronic acid (0.0396 mol) in methanol (41ml) were added to a mixture of 5-bromo-2-furancarboxaldehyde (0.0322 mol) and Pd(PPh₃)₄ (0.0009 mol) in methylphenyl (166ml) under N₂ flow. The mixture was stirred and refluxed for 4 hours and extracted with EtOAc. The precipitate was filtered off and dried. Yielding: 2.76g intermediate 23 (43%).



- A mixture of methyl-6-(1-methylhydrazino)-2,4(1H,3H)-pyrimidinedione (0.0088 mol) and intermediate 23 (0.0088 mol) in EtOH (50ml) was stirred and refluxed for 5 hours. The precipitate was filtered off and dried. Yielding: 2.07g intermediate 24 (67%).

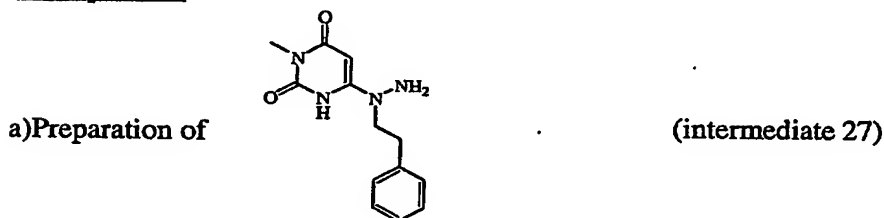


A mixture of intermediate 25 (0.0059 mol) and Raney Nickel (2.07g) in $\text{NH}_3/\text{CH}_3\text{OH}$ 7N (100ml) was hydrogenated at room temperature for 4 hours under a 3 bar pressure of H_2 , then filtered over celite. The filtrate was evaporated. Yielding: 2.09g intermediate 25 (>100%).

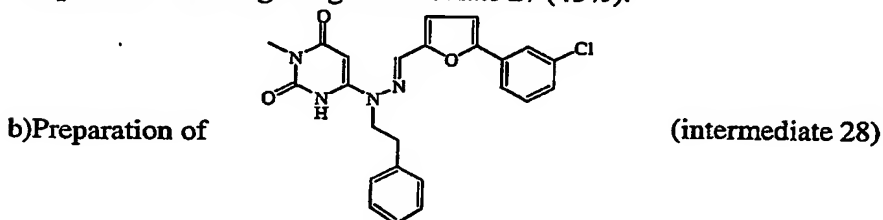


- 5 Bis(1,1-dimethylethyl) ester dicarbonic acid (0.0059 mol) was added portionwise at 0°C to a mixture of intermediate 25 (0.0059mol) and Et_3N (0.0059 mol) in CH_2Cl_2 (21ml). The precipitate was filtered off and dried. Yielding: 2.68g intermediate 26 (>100%).

Example A10



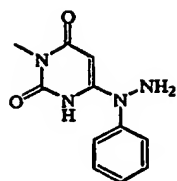
- 10 A mixture of 6-chloro-3-methyl-2,4(1H,3H)-pyrimidinedione (0.0195 mol) and 1-(2-Phenylethyl)hydrazine (0.044 mol) in EtOH (50ml) was stirred and refluxed for 5 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95/5; 15-35 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 2.2g intermediate 27 (43%).



- 15 A mixture of intermediate 27 (0.0041 mol) and 5-(3-chlorophenyl)- 2-furancarboxaldehyde (0.0041 mol) in EtOH (11ml) was stirred and refluxed for 5 hours. The precipitate was filtered off and dried. Yielding: 1.58g intermediate 28 (85%).

Example A11

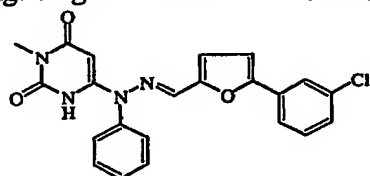
b) Preparation of



(intermediate 29)

A mixture of 6-Chloro-3-methyluracil (0.0622 mol) and phenylhydrazine (0.137 mol) in C (100ml) was stirred and refluxed for 3 hours, then filtered. This fraction was washed with hot EtOH and dried. The mother layer was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 94/6; 15-35μm). Two fractions were collected and the solvent was evaporated. Yielding: 8.5g intermediate 29 (80%).

c) Preparation of

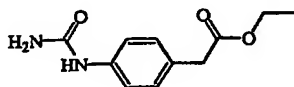


(intermediate 30)

A mixture of intermediate 29 (0.005 mol) and 5-(3-chlorophenyl)-2-furaldehyde (0.0057 mol) in EtOH (20ml) was stirred and refluxed for 1 hour, then brought to room temperature. The precipitate was filtered off and dried. Yielding: 1.8g intermediate 30.

10 Example A12

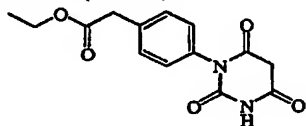
a) Preparation of



(intermediate 31)

A mixture of ethyl-2-(4-aminophenyl)acetate (0.161 mol), KOCN (0.322 mol) and TFA (0.225 mol) in toluene (250ml) was stirred at 60°C for 24 hours, then brought to room temperature and filtered. The precipitate was washed with H₂O, then with diethyl ether and dried under a vacuo. Yielding: intermediate 31 (100%).

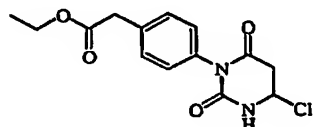
b) Preparation of



(intermediate 32)

A mixture of intermediate 31 (0.223 mol), diethyl malonate (0.223 mol) and EtONa/EtOH 21% (0.234 mol) in EtOH (500ml) was stirred and refluxed for 4 days, then brought to room temperature and the solvent was evaporated. The residue was taken up in ice water, acidified with HCl 3N, taken up in CH₂Cl₂ and washed with H₂O. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 27.8g intermediate 32 (62%).

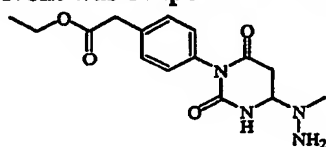
c) Preparation of



(intermediate 33)

H₂O (0.258 mol) was added dropwise slowly to a mixture of intermediate 33 (0.0957 mol) and POCl₃ (1.197 mol). The mixture was stirred and refluxed for 30 minutes, then brought to room temperature and the solvent was evaporated till dryness. Ice water was added. The mixture was extracted twice with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 94/6/0.1 to 90/10/0.2; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 8.5g intermediate 33 (28%) .

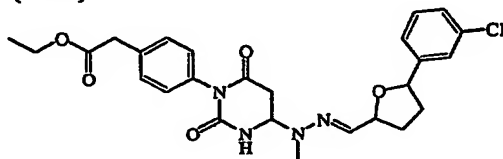
d)Preparation of



(intermediate 34)

A mixture of intermediate 34 (0.029 mol) and methylhydrazine (0.038 mol) in EtOH (85ml) was stirred and refluxed for 6 hours, cooled to room temperature and stirred at this temperature overnight. A precipitate was filtered off, washed with Et₂O and dried. Yielding : 7.7g of intermediate 34 (82%).

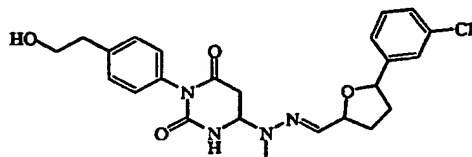
e)Preparation of



(intermediate 35)

A mixture of intermediate 34 (0.0109 mol) and 5-(3-chlorophenyl)-2-furaldehyde (0.0109 mol) in C (70ml) was stirred and refluxed for 1 hour then cooled to room temperature. A precipitate was filtered off and washed by EtOH and Et₂O then dried. Yielding : 4.3g of intermediate 35 (76%).

f)Preparation of

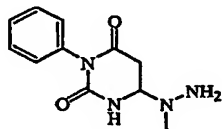


(intermediate 36)

A solution of intermediate 35 (0.0078 mol) in THF (80ml) was stirred and refluxed. KBH₄ (0.039 mol) and LiCl (0.039 mol) were added portionwise. The mixture was stirred and refluxed 24 hours, cooled to room temperature, poured out into ice water and extracted with CH₂Cl₂. A precipitate was crystallized in the organic layer, filtered off and dried. 0.3g of was taken up in a little quantity of MeOH, CH₂Cl₂ and DIPE. The precipitate was filtered off and dried. Yielding : 0.2g of intermediate 36.

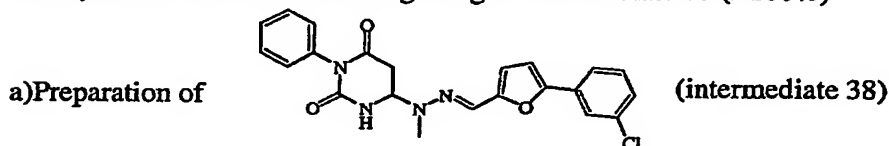
Example A13

a)Preparation of



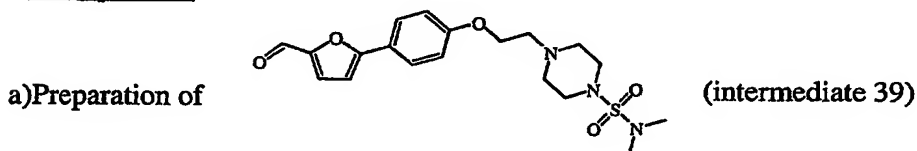
(intermediate 37)

A mixture of 6-chloro-3-phenyl-2,4(1H,3H)-Pyrimidinedione (0.0179 mol) and methylhydrazine (0.039 mol) in EtOH (40ml) was stirred and refluxed for 90 minutes, then cooled and stirred at room temperature for 1 hour. The precipitate was filtered, washed with diethyl ether and dried. Yielding: 4.3g of intermediate 37 (>100%)

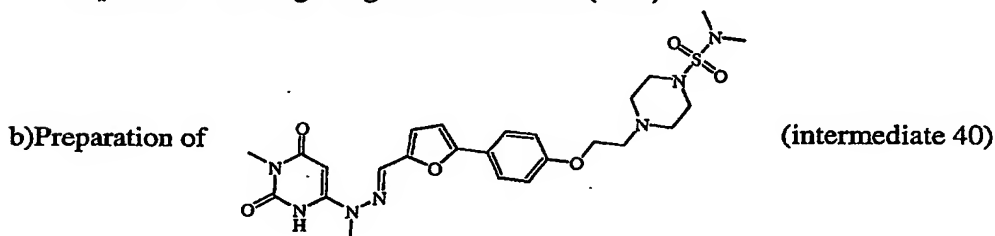


5 A mixture of intermediate 37 (0.0053 mol) and 5-(3-chlorophenyl)-2-furaldehyde (0.0053 mol) in EtOH (15ml) was stirred and refluxed for 2 hours, then cooled to room temperature, cooled to 5°C in a bath of ice. The precipitate was filtered, washed with diethyl ether and dried. Part of this fraction (0.3g) was crystallized from EtOH. The precipitate was filtered, washed with diethyl ether and dried. Yielding: 0.2g intermediate 38.

Example A16



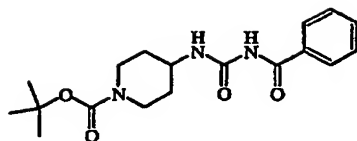
15 4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-Pyridine (0.0092 mol) was added dropwise at 5°C to a mixture of 5-(4-hydroxyphenyl)-2-Furancarboxaldehyde (0.007 mol), 4-(2-hydroxyethyl)-N,N-dimethyl-1-Piperazinesulfonamide (0.0085 mol) and PPh₃ (0.0121 mol) in THF. The mixture was stirred at 5°C for 2 hours, poured out into H₂O, then into HCl 3N. The mixture was washed with EtOAc. The aqueous layer was basified with K₂CO₃. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. Yielding: 2.6g intermediate 39 (75%).



20 A mixture of 3-methyl-6-(1-methylhydrazino)-2,4(1H,3H)-Pyrimidinedione (0.017 mol) and intermediate 39 (0.0373 mol) in EtOH (50ml) was stirred and refluxed for 2 hours, then cooled. The precipitate was filtered, rinsed with EtOH and dried. Yielding: 2.12g intermediate 40 (59 %).

Example A17

a) Preparation of

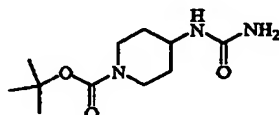


(intermediate 41)

4-amino-1-Boc-piperidine (0.0484 mol) was added portionwise at 0°C to a mixture of benzoyl isocyanate (0.0533 mol) in CH₂Cl₂ (280 ml) under N₂ flow. The mixture was stirred at room temperature for 3 hours. The solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried. Yielding: 7.75 g of intermediate 41 (46%).

5

b) Preparation of

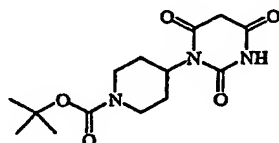


(intermediate 42)

A mixture of intermediate 41 (0.0223 mol) and NaOH (0.38 mol) in CH₃OH (100 ml) and H₂O (100 ml) was stirred at room temperature for 12 hours, then stirred and refluxed for 1 hour and brought to room temperature. CH₃OH was evaporated. The precipitate was filtered, washed with H₂O and dried. Yielding: 4.46 g of intermediate 42 (82%).

10

c) Preparation of

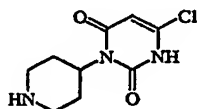


(intermediate 43)

A mixture of intermediate 42 (0.0183 mol), diethyl malonate (0.02 mol) and EtONa/EtOH 21% (0.02 mol) in EtOH (60 ml) was stirred and refluxed for a week-end, then brought to room temperature and the solvent was half evaporated. The mixture was taken up in H₂O. HCl 3N was added till pH 5.5 was obtained. The mixture was extracted twice with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was taken up in cyclohexane. The precipitate was filtered off and dried. Yielding: 5.4 g of intermediate 43 (94%).

15

d) Preparation of



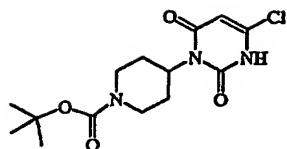
(intermediate 44)

H₂O (0.0459 mol) was added dropwise slowly at room temperature to a mixture of intermediate 43 (0.017 mol) and POCl₃ (0.21 mol). The mixture was stirred and refluxed for 30 minutes, then brought to room temperature and the solvent was evaporated. The residue was taken up in ice. K₂CO₃ was added till pH 7 obtained. The mixture was washed with CH₂Cl₂ and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried. Yielding: 3.63g of intermediate 44.

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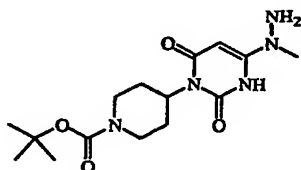
e) Preparation of



(intermediate 45)

A mixture of intermediate 44 (0.017 mol) and Boc-anhydride (0.026 mol) in CH_2Cl_2 (70 ml) and CH_3OH (15 ml) was stirred at room temperature for 12 hours. H_2O was added. The mixture was decanted. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . Activated carbon was added. The mixture was filtered over celite. The solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried. Yielding: 1.7g of intermediate 45.

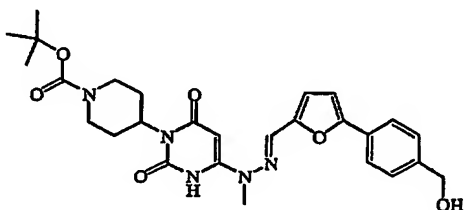
f) Preparation of



(intermediate 46)

A mixture of intermediate 45 (0.0052 mol) and methylhydrazine (0.012 mol) in EtOH (20 ml) was stirred and refluxed for 1 hours, then brought to room temperature. The solvent was evaporated. Yielding: 1.76 g of intermediate 46.

g) Preparation of

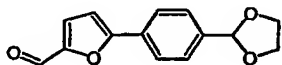


(intermediate 47)

A mixture of intermediate 46 (0.0285 mol) and 5-(4-hydroxyphenyl)-2-furancarboxaldehyde (0.0285 mol) in EtOH (150 ml) was stirred and refluxed for 2 hours, then brought to room temperature and the solvent was evaporated. The residue was taken up in CH_2Cl_2 . The organic layer was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (16 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 60/40; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 7.8 g of intermediate 47 (52%).

20 Example A18

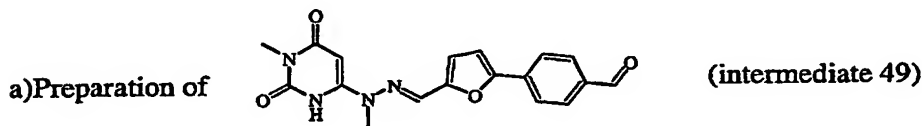
a) Preparation of



(intermediate 48)

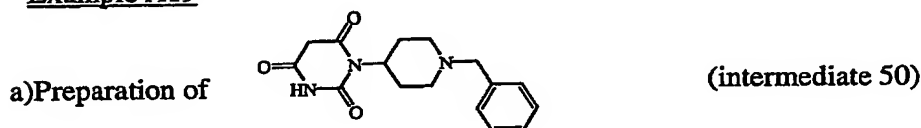
A mixture of 2-(4-bromophenyl)-1,3-dioxolane (0.061 mol), 5-(tributylstannyl)furan-2-carbaldehyde (0.079 mol) and $\text{Pd}(\text{PPh}_3)_4$ (3.5 g) in toluene (200 ml) was stirred and refluxed for 3 hours, then brought to room temperature and filtered over celite. Celite was washed with

CH_2Cl_2 . The filtrate was evaporated. The residue (53 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2 100; 15-35 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 7.2g intermediate 48 (48%).



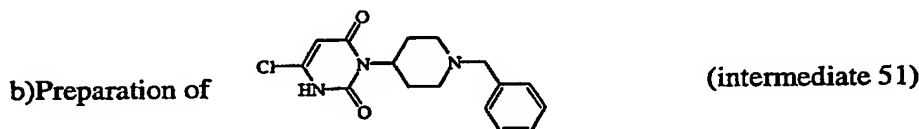
- 5 A mixture of 4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-Pyridine (0.026 mol) and intermediate 48 (0.03 mol) in EtOH (100 ml) was stirred and refluxed for 2 hours, then brought to room temperature. The precipitate was filtered, washed with EtOH and dried. Yielding: 8.25g of intermediate 49 (90%).

10 Example A19



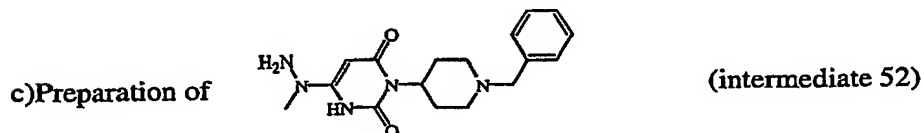
A mixture of [1-(phenylmethyl)-4-piperidinyl]-urea (0.0248 mol), diethyl malonate (0.0248 mol) and EtONa/EtOH (0.0248 mol) in EtOH (90 ml) was stirred and refluxed for 6 days. The solvent was evaporated till dryness. The residue was taken up in H_2O . HCl 1N was added till pH 7 was obtained. The solvent was evaporated till dryness. Yielding: 7.5g of intermediate 50

- 15 (> 100%).



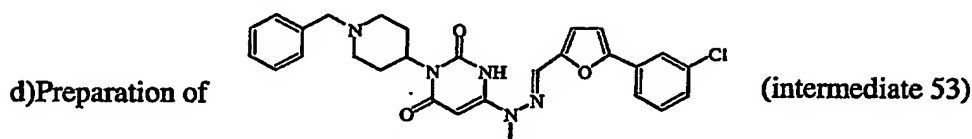
H_2O (0.0755 mol) was added dropwise very slowly to a mixture of intermediate 50 (0.0282 mol) and POCl_3 (0.355 mol). The mixture was stirred and refluxed for 30 minutes. The solvent was evaporated till dryness. The residue was poured out on ice and basified with

- 20 K_2CO_3 . The residue was dried. Yielding: 6.56g of intermediate 51 (73%).



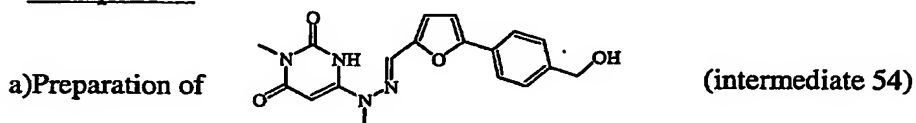
A mixture of intermediate 51 (0.0205 mol) and methylhydrazine (0.041 mol) in EtOH (66 ml) was stirred and refluxed for 3 hours and filtered. The filtrate was evaporated till dryness. The residue was taken up in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ (90/10/0.5) and purified over SiO_2 (35-70 μm).

The pure fractions were collected and the solvent was evaporated. Yielding: 2.65g of intermediate 52 (39%).

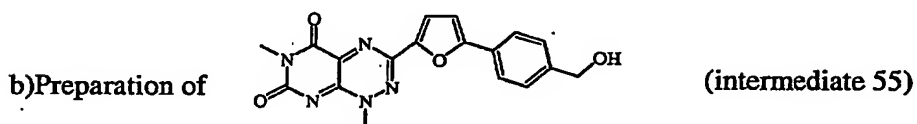


A mixture of intermediate 52 (0.0034 mol) and 2-(3-chlorophenyl)-2-furancarboxaldehyde (0.0034 mol) in EtOH (11 ml) was stirred and refluxed for 5 hours. The precipitate was filtered off and dried. Yielding: 1.2g of intermediate 53 (68%).

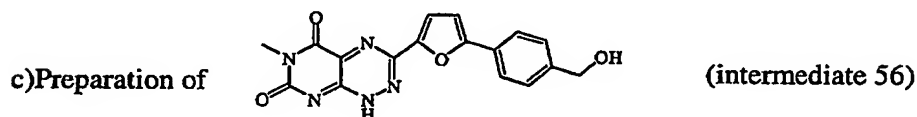
Example A20



A mixture of 5-(4-hydroxymethylphenyl)-2-furancarboxaldehyde (0.0133 mol) and 3-methyl-6-(1-methylhydrazino)-2,4(1H,3H)-Pyrimidinedione (0.0133 mol) in EtOH (81 ml) was stirred and refluxed for 2 hours. The precipitate was filtered, washed twice with EtOH and dried with diethylether. Yielding: 4.1g of intermediate 54 (87%).



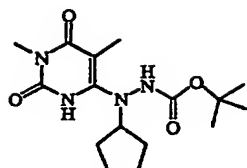
NaNO₂ (0.0033 mol) was added at 5°C to a mixture of intermediate 54 (0.0022 mol) in AcOH (8ml) and H₂O (0.8ml). The mixture was brought to room temperature and stirred overnight. Diethyl ether was added. The precipitate was filtered off and dried. Yielding: 6g of intermediate 55 and its nitrosoderivative



A mixture of intermediate 55 (0.0158 mol) and its nitrosoderivative (0.0158 mol) in DMF (120 ml) was stirred at 90°C for 2 hours, then brought to room temperature. Ice and water were added. The mixture was stirred for 10 minutes. the precipitate was filtered off and dried . Yielding: 5.9g of intermediate 56 (59%).

Example A21

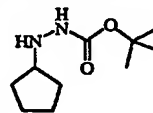
a) Preparation of



(intermediate 61)

A mixture of 6-chloro-2-hydroxy-3-methyl-5-nitro-3,5-dihydropyrimidine-4-one (0.114 mol) in

CH_2Cl_2 (250 ml) was stirred at room temperature and a solution of

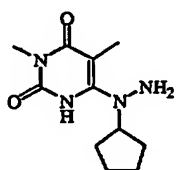


(t-

butoxycarbonyl-cyclopentylhydrazine) (0.17 mol) in CH_2Cl_2 (50 ml) was added dropwise.

- After addition of t-butoxycarbonyl-cyclopentylhydrazine, the mixture was stirred at room temperature for 4 hours. The precipitate was filtered off, and washed with DIPE and dried under vacuum at 50°C. The residual fraction was stirred in a mixture of CH_2Cl_2 / DIPE (8/2). The precipitate was filtered off, washed and dried under vacuum at 50°C. Yielding 36,4g of intermediate 61 (87%).

b) Preparation of



(intermediate 62)

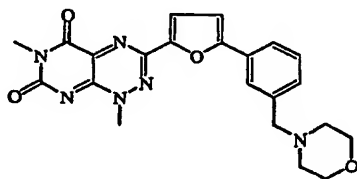
- A solution of intermediate 61 (0.054 mol), CF_3COOH (40 ml) and CH_2Cl_2 (160 ml) was stirred at room temperature for 4 hours. The reaction was completed and the solvent was removed under reduced pressure. The residual fraction was stirred in DIPE / 2-propanol (1/1). The precipitate was filtered off, washed and dried under vacuum at 50°C. Yielding: 13,1 g of intermediate 62 (90%).

15

B. Preparation of the compounds

Example B1

Preparation of



(compound 1)

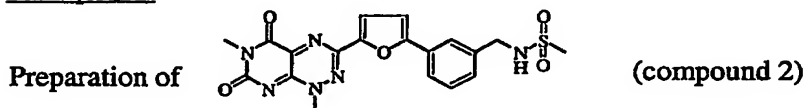
- a) NaNO_2 (0.0113 mol) was added portionwise at 5°C to a mixture of intermediate 4 (0.0075 mol) in AcOH (32ml) and H_2O (1.6ml). The mixture was brought to room temperature and stirred overnight. Diethyl ether was added. The precipitate was filtered off and dried. Yielding: 6g compound 1 and its nitrosoderivative (global yield: >100%). This product was used directly in the next reaction step.

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b) A mixture of (0.0011 mol) compound 1 and the nitrosoderivative thereof (0.001 mol) and 1,4-dimercapto-2,3-butanediol (0.0033 mol) in EtOH (10ml) was stirred at room temperature for a week-end. The precipitate was filtered, washed twice with EtOH/H₂O then washed three times with CH₃OH/diethyl ether and dried. Yielding: 0.337g compound 1 (34%)

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Example B2



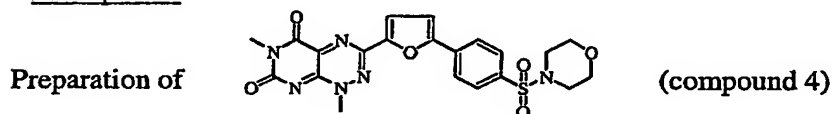
a) A mixture of intermediate 6 (0.0028 mol) and NaNO₂ (0.0042 mol) in H₂O (0.7ml) and AcOH (12ml) was stirred at room temperature for 36 hours, then diluted in diethyl ether. The precipitate was filtered off and dried. Yielding: 1.3g compound 2 and its nitrosoderivative (>100%).

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b) A mixture of (0.0003 mol) compound 2 and its nitrosoderivative (0.0003 mol) and 1,4-dimercapto-2,3-butanediol (0.0013 mol) in EtOH (10ml) was stirred at room temperature for 24 hours. 1,4-Dimercapto-2,3-butanediol (0.0013 mol) was added again. The mixture was stirred for 6 days. The precipitate was filtered off and dried. Yielding: 0.162g nitrosoderivative. This fraction was taken up in EtOH/CH₃OH. The precipitate was filtered off and dried. Yielding: 0.11g compound 2 (37%).

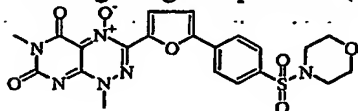
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Example B3



a) NaNO₂(0.0047 mol) was added at 5°C to a mixture of intermediate 8 (0.031 mol) in AcOH (15ml) and H₂O (0.7ml). The mixture was brought to room temperature and stirred at room temperature for 5 hours. Diethyl ether was added. The precipitate was filtered off and dried. Yielding: 1.8g compound 4 (quantitative) and the nitrosoderivative

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(intermediate 9) thereof. The product was used without further purification in the next reaction step.

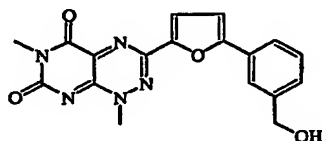
b) A mixture of (0.0010 mol) compound 4 and its nitrosoderivative(0.0010) and 1,4-dimercapto-2,3-butanediol (0.0029 mol) in EtOH (20ml) was stirred at room temperature for 3 days. 1,4-dimercapto-2,3-butanediol (0.0029 mol) was added. The mixture was stirred at room temperature for 4 days. The precipitate was filtered off and dried. Yielding 0.8g fraction 1. A solution of 1,4-dimercapto-2,3-butanediol (0.0029 mol) in EtOH (20ml) was added to this

25

fraction. The mixture was stirred at room temperature for 2 days. The precipitate was filtered off and dried. Yielding: 0.6g fraction 2. This fraction was washed with diethyl ether. The precipitate was filtered off and dried. Yielding: 0.5g fraction 3. This fraction was dried at 50°C under a vacuo for 6 hours. Yielding: 0.258g fraction 4. This fraction was dried at 80°C under a vacuo for 6 hours. Yielding: 0.242g compound 4.

Example B4

Preparation of



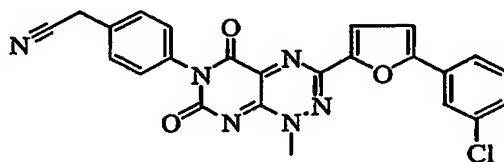
(compound 5)

a) A mixture of intermediate 2 (0.0033 mol) in AcOH (12ml) and H₂O (0.6ml) was cooled to 0°C. KNO₂ (0.0050 mol) was added portionwise. The mixture was brought to room temperature and stirred at room temperature for 24 hours. Diethyl ether was added. The precipitate was filtered off and dried. Yielding: 1.5g compound 5 and its nitrosoderivative. The product was used without further purification in the next reaction step.

b) A mixture of (0.002 mol) compound 5 and its nitrosoderivative (0.0020 mol) and 1,4-dimercapto-2,3-butanediol (0.0059 mol) in methanol (15ml) was stirred at room temperature for 48 hours. The precipitate was filtered, washed with H₂O, with EtOH then with diethyl ether and dried. The residue was taken up in CH₃OH/THF/CH₂Cl₂. The precipitate was filtered off and dried. Yielding: 0.65g compound 5 (46%).

Example B5

Preparation of



(compound 6)

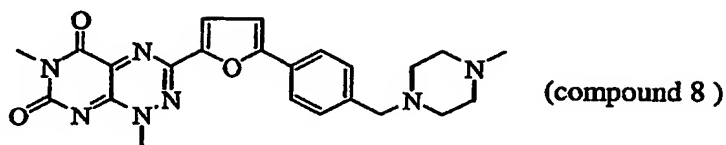
a) NaNO₂ (0.0026 mol) was added at 5°C to a mixture of intermediate 16 (0.0017 mol) in AcOH (8ml) and H₂O (0.8ml). The mixture was brought to room temperature, then stirred for 20 days. Diethyl ether was added. The precipitate was filtered off and dried. Yielding: 1.5g compound 6 (>100%) and the nitrosoderivative thereof.

b) A mixture of compound 6 (0.0015 mol) and its nitrosoderivative (0.0015 mol) and 1,4-dimercapto-2,3-butanediol (0.0046 mol) in EtOH (15ml) was stirred at room temperature for 5 days. The precipitate was filtered, washed twice with EtOH, then washed twice with H₂O, then with EtOH, diethyl ether and dried. This fraction was taken up in H₂O, washed with EtOH/THF and dried with diethyl ether. This fraction was taken up in H₂O, washed with methanol and

dried with diethyl ether. This fraction was washed with H₂O/EtOH and dried with diethyl ether. Yielding: 0.21g compound 6 (15%).

5 Example B6

Preparation of

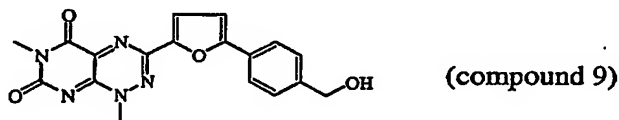


a) NaNO₂ (0.0082 mol) was added at 5°C to a mixture of intermediate 22 (0.0027 mol) in AcOH (12ml) and H₂O (1.2ml). The mixture was brought to room temperature and stirred overnight. Diethyl ether was added. The precipitate was filtered off and dried. Yielding: 1.6g compound 8 and the nitrosoderivative thereof (>100%). This product was used directly in the next reaction step.

b) A mixture of compound 8 (0.0013 mol) and its nitrosoderivative (0.0013 mol) and 1,4-dimercapto-2,3-butanediol (0.0051 mol) in ethanol (10ml) was stirred at room temperature for 10 days. The precipitate was filtered, washed with EtOH, then with diethyl ether and dried. The residue (1g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 80/20; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.19g fraction 1 and 0.6g fraction 2 (38%). Part of F2 (0.25g) was washed with K₂CO₃ 10% and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. Yielding: 0.08g compound 9.

20 Example B7

Preparation of

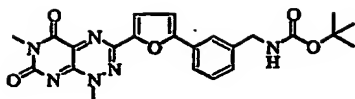


a) NaNO₂ (0.0033 mol) was added at 5°C to a mixture of intermediate 21 (0.0022 mol) in AcOH (8ml) and H₂O (0.8ml). The mixture was brought to room temperature and stirred overnight. The precipitate was filtered. The filtrate was washed with diethyl ether and dried. Yielding: 1.2g compound 9 and the nitrosoderivative thereof. This product was used without further purification.

b) A mixture of compound 9 (0.0015 mol) and its nitrosoderivative (0.0015 mol) and 1,4-dimercapto-2,3-butanediol (0.0047 mol) in methanol (10ml) was stirred at room temperature for 4 days. The precipitate was filtered, washed with H₂O, twice with EtOH and dried with diethyl ether. Yielding: compound 10 (58%).

Example B8

Preparation of



(compound 10)

a) NaNO_2 (0.0065 mol) was added portionwise at 0°C to a mixture of intermediate 26 (0.0059 mol) in AcOH (29ml) and H_2O (1.06ml). The mixture was stirred at room temperature overnight.

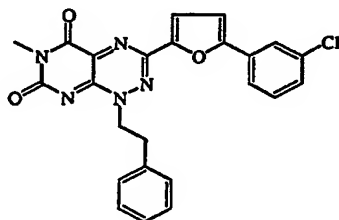
5 The precipitate was filtered off and dried. Yielding: 2.06g compound 10 (74%).

b) A mixture of compound 10 (0.0021 mol) and its nitrosoderivative (0.0021 mol) and 1,4-dimercapto-2,3-butanediol (0.0087 mol) in EtOH (178ml) and THF (38ml) was stirred at room temperature for 5 days. The precipitate was filtered off and dried. Yielding: 1.2g compound 10 (59%).

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Example B9

Preparation of



(compound 11)

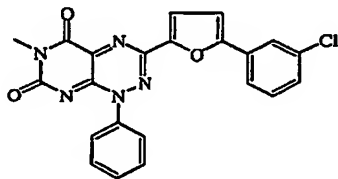
a) NaNO_2 (0.0033 mol) was added portionwise at 0°C to a mixture of intermediate 28 (0.003 mol) in AcOH (16ml) and H_2O (0.55ml). The mixture was stirred at room temperature overnight. The precipitate was filtered off and dried. Yielding: 1.46g nitrosoderivative(>100%).

15 b) A mixture of this nitrosoderivative (0.003 mol) and 1,4-dimercapto-2,3-butanediol (0.0061 mol) in EtOH (125ml) and THF (26ml) was stirred at room temperature for 3 days. The precipitate was filtered and purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 80/20; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.65g compound 11 (46%).

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Example B10

Preparation of



(compound 12)

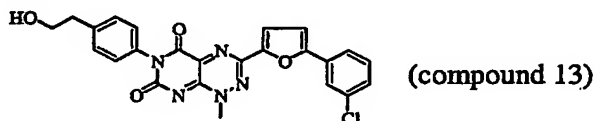
a) NaNO_2 (0.0045 mol) was added at a temperature between 0 and 5°C to a mixture of intermediate 30 (0.0037 mol) in H_2O (0.65ml) and AcOH (18ml). The mixture was stirred at

room temperature for 7 days. The precipitate was filtered, washed with diethyl ether and dried. Yielding: 1.24g compound 12 and the nitrosoderivative thereof

b) A mixture of compound 12 (0.0014 mol) and its nitrosoderivative (0.0014 mol) and 1,4-dimercapto-2,3-butanediol (0.0083 mol) in methanol (15ml) was stirred at room temperature for 3 days. The precipitate was filtered, washed with CH₃OH, then with H₂O, then with methanol and dried. The residue (1g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.3g compound 13 (global yield: 58%).

10 Example B11

Preparation of

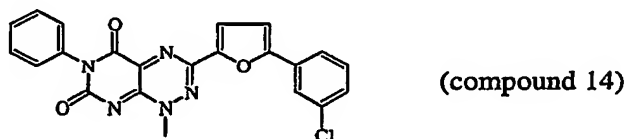


a) A mixture of intermediate 36 (0.0032 mol) in AcOH (15ml) and H₂O (1.5ml) was cooled to 5°C. NaNO₂ (0.0097 mol) was added. The mixture was brought to room temperature, then stirred at room temperature overnight. The precipitate was filtered, washed with EtOH, then with diethyl ether and dried. Yielding: compound 13 and the nitrosoderivative thereof. This product was used directly in the next reaction step.

b) A mixture of compound 13 (0.0018 mol) and its nitrosoderivative (0.0018 mol) and 1,4-dimercapto-2,3-butanediol (0.0056 mol) in EtOH (40ml) was stirred at room temperature for 36 hours. The precipitate was filtered, washed twice with EtOH, then with diethyl ether and dried. Yielding: 1.1g fraction 1 (61%). This fraction was dried at 40°C in a vacuo. Yielding: 0.33g fraction 2. This fraction was dried in a vacuo. Yielding: 0.3g fraction 3. This fraction was taken up in diethyl ether. The precipitate was filtered off and dried. Yielding: 0.29g fraction 4. This fraction was dried in a vacuo. Yielding: 0.28g fraction 5. This fraction was washed with H₂O, taken up in EtOH, washed again and dried. Yielding: 0.28g compound 13.

25 Example B12

Preparation of



a) NaNO₂ (0.0064 mol) was added at 5°C to a mixture of intermediate 36 (0.0042 mol) in AcOH (18ml) and H₂O (0.9ml). The mixture was stirred at room temperature for 48 hours and poured out into H₂O. The precipitate was filtered, washed with H₂O and dried. The residue was taken up in CH₂Cl₂ and washed with H₂O. The organic layer was separated, dried (MgSO₄),

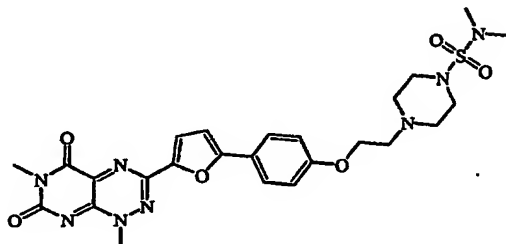
filtered, and the solvent was evaporated. Yielding: 1.6g compound 14 and the nitrosoderivative thereof

(85%).

- 5 b) A mixture of compound 14 (0.0018 mol) and its nitrosoderivative (0.0018 mol) and 1,4-dimercapto-2,3-butanediol (0.0072 mol) in EtOH (30ml) was stirred at room temperature for 15 days. The precipitate was filtered, washed with diethyl ether and dried. The residue (1g) was taken up in EtOH (hot). The precipitate was filtered, washed with EtOH, then with diethyl ether and dried. Yielding: 0.6g compound 14 (38%).

10 Example B13

Preparation of

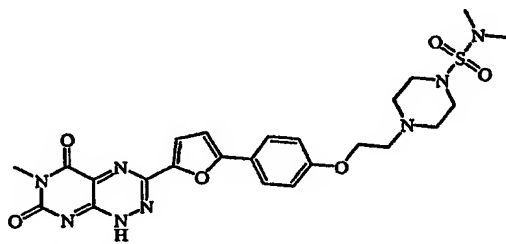


(compound 15)

- a) NaNO_2 (0.0056 mol) was added at 5°C to a mixture of intermediate 40 (0.0037 mol) in AcOH (20ml) and H_2O (0.65ml). The mixture was stirred at room temperature for 5 hours. DIPE was added. The precipitate was filtered off and dried. Yielding: 2.6g of compound 15 and its nitrosoderivative.

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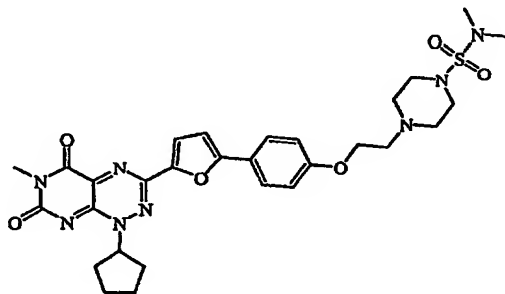
Preparation of



(intermediate 57)

- b) A mixture of compound 15 (0.0018 mol) and its nitrosoderivative (0.0018 mol) in DMF (20 ml) was stirred at 100°C for 1 hour, then brought to room temperature. The precipitate was diluted in H_2O , filtered off and dried. Yielding: 1.8g of intermediate 57

Preparation of

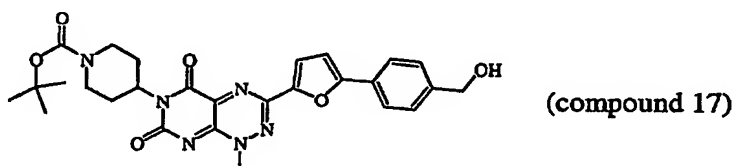


(compound 16)

- 5 c) A mixture of intermediate 57 (0.0037 mol), bromocyclopentane (0.017 mol) and K_2CO_3 (0.011 mol) in dioxane (185 ml) was stirred at at 120°C for 2 days, then brought to room temperature. The solvent was evaporated. The residue was taken up in H_2O . The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (2.4g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ 98/2$; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.069 of compound 16 (2.6 %).

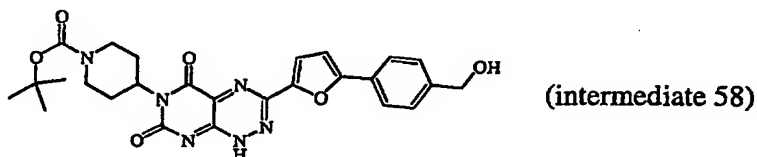
Example B14

Preparation of



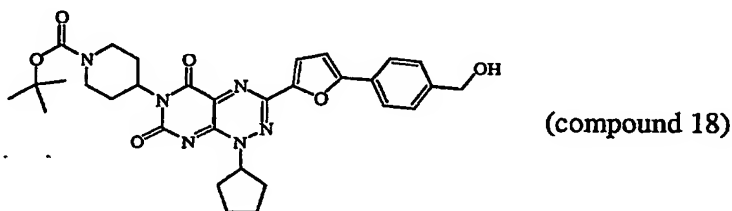
- 10 a) $NaNO_2$ (0.0217 mol) was added at 5°C to a mixture of intermediate 47 (0.0145 mol) in AcOH (76ml) and H_2O (3.8ml). The mixture was stirred at room temperature for 6 hours. DIPE was added. The precipitate was filtered off and dried. Yielding: 6.4g of compound 17 and its nitrosoderivative.

Preparation of



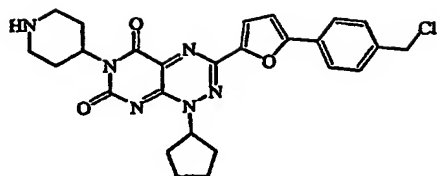
- 15 b) A mixture of compound 17 (0.0057 mol) and its nitrosoderivative (0.0057 mol) in DMF (60 ml) was stirred at 100°C for 30 minutes, then brought to room temperature. The precipitate was diluted in ice and H_2O , filtered off and dried. Yielding: 7.1g of intermediate 58

Preparation of



- 20 c) A mixture of intermediate 58 (0.0019 mol), bromocyclopentane (0.0076 mol) and K_2CO_3 (0.0057 mol) in dioxane (100 ml) was stirred and refluxed for 7 hours, then brought to room temperature. The solvent was evaporated. The residue was taken up in H_2O . The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (2.4g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ 98/2$; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.1g of compound 18 (27 %).
- 25

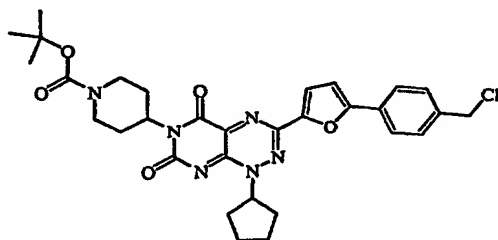
Preparation of



(compound 19)

d) SOCl_2 (0.0067 mol) was added at room temperature to a mixture of compound 18 (0.0016 mol) in CH_2Cl_2 (20 ml). The mixture was stirred at room temperature for 4 hours. The solvent was evaporated. Yielding: 19 of compound 19. This product was used directly in the next reaction step.

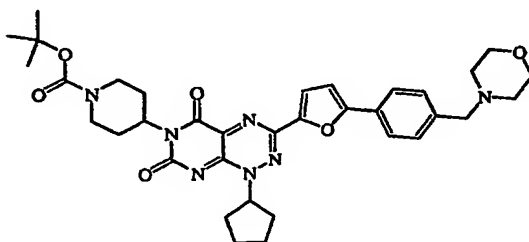
Preparation of



(compound 20)

e) $(\text{Boc})_2\text{O}$ (0.0029 mol) was added portionwise to a mixture of compound 19 (0.0019 mol) in CH_2Cl_2 (50 ml). The mixture was stirred at room temperature for 1 hour. Ice and water were added. The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated. yielding: 1.15g of compound 20. This product was used directly in the next reaction step.

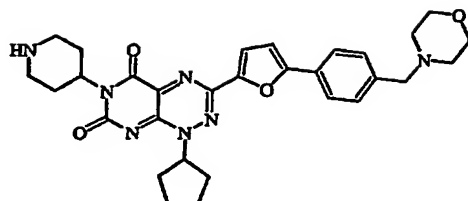
Preparation of



(compound 21)

f) A mixture of compound 20 (0.0019 mol), morpholine (0.0038 mol) and Et_3N (0.0028 mol) in CH_3CN was stirred at room temperature for 12 hours, then at 80°C for 3 hours, then brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The organic layer was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (1.6g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/98/2$; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.15g of compound 21 (16 %).

Preparation of



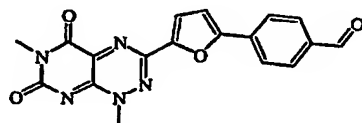
(compound 22)

g) HCl/isopropanol 5/6N (0.2 ml) was added to a mixture of compound 21 (0.0001 mol) in isopropanol (1ml). The mixture was stirred at 60°C for 6 hours, then brought to room temperature. The precipitate was filtered off and dried with diethylether. Yielding: 0.073g of compound 22 (76%).

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Example B15

Preparation of

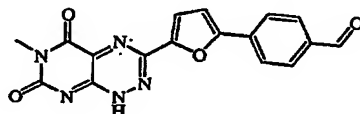


(compound 23)

a) NaNO_2 (0.035 mol) was added at 5°C to a mixture of intermediate 49 (0.0234 mol) in AcOH (100ml) and H_2O (4.8ml). The mixture was stirred at room temperature for 18 hours. DIPE was added. The precipitate was filtered off and dried. Yielding: 9.1g of compound 23 and its nitrosoderivative.

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Preparation of

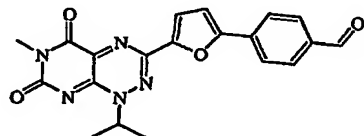


(intermediate 59)

b) A mixture of compound 23 (0.0117 mol) and its nitrosoderivative (0.0117 mol) in DMF (70 ml) was stirred at 90°C for 2 hours, then brought to room temperature. The precipitate was diluted in ice and H_2O , filtered off and dried. Yielding: 7.75g of intermediate 59

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Preparation of

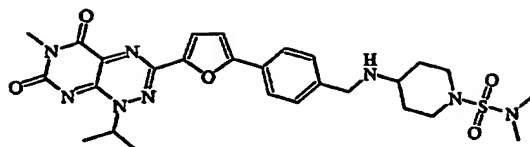


(compound 24)

c) A mixture of intermediate 59 (0.0091 mol), 2-iodopropane (0.0412 mol) and K_2CO_3 (0.0394 mol) in dioxane (400 ml) was stirred and refluxed at 120°C for 48 hours, then brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated. The residue (3.2g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/98/2$; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.7g of compound 24 (20 %).

20

Preparation of

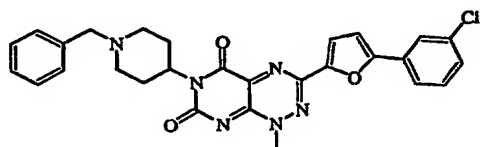


(compound 25)

d) A mixture of compound 24 (0.0016 mol), 4-amino-1-dimethylaminosulfonyl-piperidine (0.002 mol) and NEt_3 in EtOH (50 ml) was stirred at 60°C for 3 hours, then brought to room temperature. NaBH_4 (0.0033 mol) was added portionwise. The mixture was stirred at room temperature for 1 hour, poured out into H_2O and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was taken up in EtOH. The precipitate was filtered off and dried. Yielding: 0.867g of compound 25 (89%).

Example B16

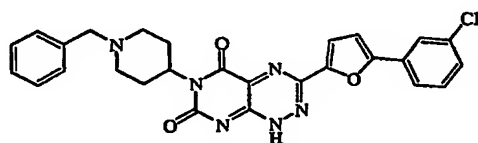
Preparation of



(compound 26)

a) NaNO_2 (0.0021 mol) was added at 0°C to a mixture of intermediate 53 (0.0019 mol) in AcOH (10ml) and H_2O (0.36ml). The mixture was stirred at room temperature for 24 hours, poured out on ice, basified with K_2CO_3 and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ / 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.19g of compound 26 (19 %).

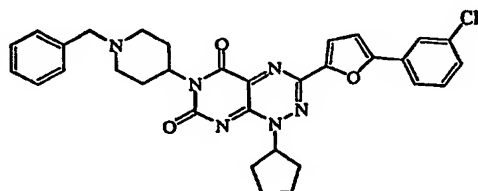
Preparation of



(intermediate 60)

b) A mixture of compound 26 (0.013 mol) and its nitrosoderivative (0.013 mol) in DMF (100 ml) was stirred at 50°C for 3 hours, then brought to room temperature. The residue was taken up in diethyl ether. The precipitate filtered off and dried. Yielding: 8.54g of intermediate 60 (64%).

Preparation of



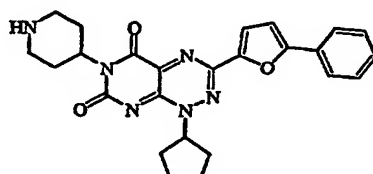
(compound 27)

c) A mixture of intermediate 60 (0.0006 mol), bromocyclopentane (0.0023 mol) and K_2CO_3 (0.0018 mol) in dioxane (30 ml) was stirred and refluxed at 120°C for 4 hours, then brought to

room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated. The residue was taken up in EtOH. The precipitate was filtered off and dried. Yielding: 0.082g of compound 27 (24 %).

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Preparation of

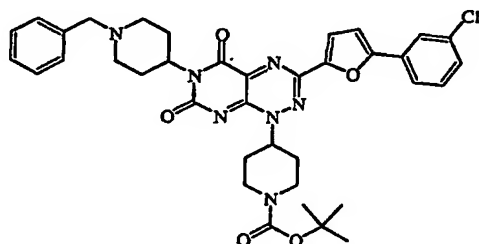


(compound 28)

d) A mixture of compound 27 (0.0008 mol) and $\text{Pd}(\text{OH})_2$ (0.04 g) in methanol (10 ml) was hydrogenated at room temperature for 50 hours under 60 Psi. The precipitate was filtered over celite. The filtrate was evaporated. The residue (0.44 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 92/8/0.1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.2g, 50%) was taken up in DIPE. The precipitate was filtered off and dried. Yielding 0.13g of compound 28).

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Preparation of

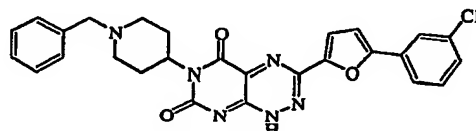


(compound 29)

e) A mixture of intermediate 60 (0.0019 mol), tert-butyl-4-iodopiperidine-1-carboxylate (0.0058 mol) and K_2CO_3 (0.0038 mol) in dioxane (50 ml) was stirred and refluxed for 48 hours then filtered. The filtrate was evaporated. The residue was taken up in H_2O and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 96/4; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.08g of compound 29 (6 %)

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Preparation of

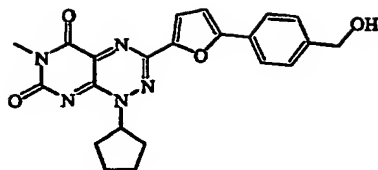


(compound 30)

f) A mixture of compound 29 (0.0001 mol) in HCl 5-6N in isopropanol (0.2 ml) and isopropanol (10 ml) was stirred at 60°C overnight. The precipitate was filtered off and dried. Yielding: 0.051g of compound 30 (60%).

Example B17

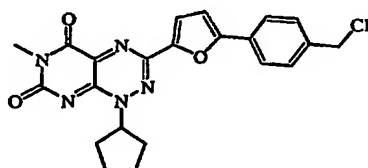
a) Preparation of



(compound 31)

A mixture of intermediate 56 (0.0051 mol), bromocyclopentane (0.023 mol) and K_2CO_3 (0.0154 mol) in dioxane (180 ml) was stirred and refluxed at 120°C for 48 hours, then brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (3.2g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. Yielding: 0.35g of compound 31 (6.8 %).

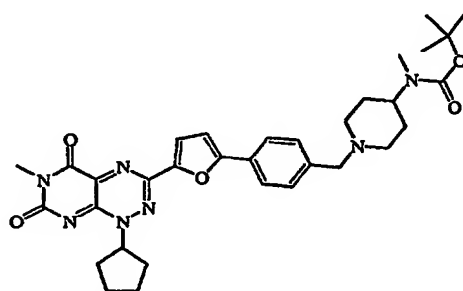
b) Preparation of



(compound 32)

$SOCl_2$ (0.0033 mol) was added at room temperature to a mixture of compound 31 (0.0008 mol) in CH_2Cl_2 (16 ml). The mixture was stirred at room temperature for 2 hours. The solvent was evaporated. Yielding: 0.36g of compound 32.

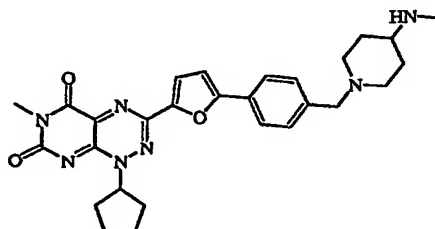
Preparation of



(compound 33)

A mixture of compound 32 (0.0034 mol), 4-N-Boc-4-N-methyl-aminopiperidine (0.0034 mol) and K_2CO_3 (0.0034 mol) in CH_3CN (50 ml) was stirred at 50°C overnight, then brought to room temperature. The solvent was evaporated yielding compound 33. This product was used directly in the next reaction step.

Preparation of

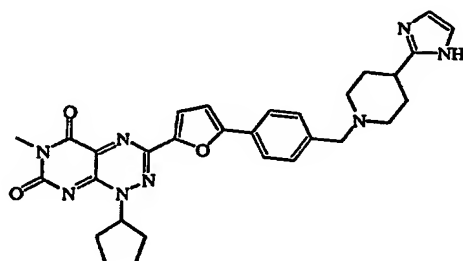


(compound 34)

- c) A mixture of compound 33 (0.0028 mol), HCl (5-6N) in isopropanol (3 ml) and isopropanol (50 ml) was heated up to reflux and stirred at 60°C for 3 hours, then brought to room temperature. The crude reaction medium was purified by HPLC. The desired fractions were collected and the organic solvent was evaporated. The water layer was neutralized with K₂CO₃ and extracted with MeOH/CH₂Cl₂ (5/95). The organic layer was dried with MgSO₄, filtered and evaporated till dryness. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried under vacuo at 50°C. Yielding 0.056g of compound 34.

Example B18

Preparation of

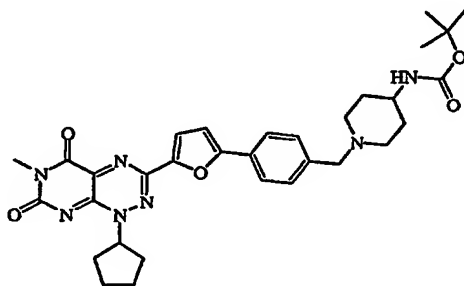


(compound 35)

- 10 A mixture of compound 32 (0.0011 mol), 4-(1H-imidazol-2-yl)-piperidine (0.0011mol) and K₂CO₃ (0.0022 mol) in CH₃CN (15 ml) was stirred and refluxed at 50°C overnight, then brought to room temperature. The crude reaction medium was purified by HPLC. The desired fractions were collected and the organic solvent was evaporated. The water layer was neutralized with K₂CO₃ and extracted with MeOH/CH₂Cl₂ (5/95). The organic layer was dried with MgSO₄, filtered and evaporated till dryness. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried under vacuo at 60°C. Yielding 0.165g of compound 35.

Example B19

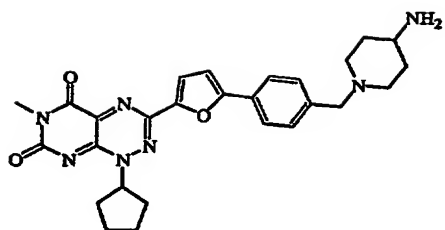
a) Preparation of



(compound 36)

- 20 A mixture of compound 32 (0.0022 mol), Boc-4-aminopiperidine (0.0022mol) and K₂CO₃ (0.0022 mol) in CH₃CN (50 ml) was stirred and refluxed at 50°C for 24 hours, then brought to room temperature. The solvent was evaporated yielding compound 36. This product was used directly in the next reaction step.

b) Preparation of

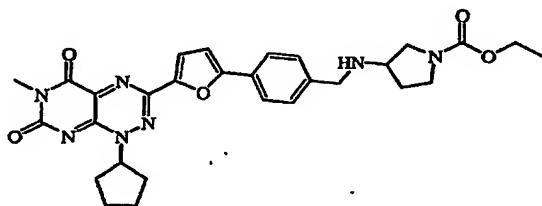


(compound 37)

A mixture of compound 36 (0.0028 mol), HCl (5-6N) in isopropanol (3 ml) and isopropanol (50 ml) was heated up to reflux and stirred at 60°C for 3 hours, then brought to room temperature. The crude reaction medium was purified by HPLC. The desired fractions were collected and the organic solvent was evaporated. The water layer was neutralized with K₂CO₃ and extracted with MeOH/CH₂Cl₂ (5/95). The organic layer was dried with MgSO₄, filtered and evaporated till dryness. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried under vacuo at 50°C. Yielding 0.056g of compound 37.

Example B20

Preparation of

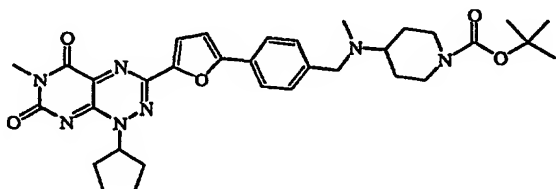


(compound 38)

A mixture of compound 32 (0.0010 mol), 1-pyrrolidinecarboxylic acid, 3-amino-, ethylester (0.0010mol) and K₂CO₃ (0.0020 mol) in CH₃CN (15 ml) was stirred and refluxed at 50°C overnight, then brought to room temperature. The crude reaction medium was purified by HPLC. The desired fractions were collected and the organic solvent was evaporated. The water layer was neutralized with K₂CO₃ and extracted with MeOH/CH₂Cl₂ (5/95). The organic layer was dried with MgSO₄, filtered and evaporated till dryness. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried under vacuo at 50°C. Yielding 0.0261g of compound 38.

Example B21

a) Preparation of



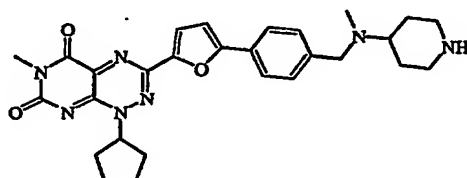
(compound 39)

A mixture of compound 32 (0.0010 mol), N-methyl-1-tert-butoxycarbonyl-4-piperidinamine (0.0010mol) and K₂CO₃ (0.0020 mol) in CH₃CN (15 ml) was stirred and refluxed at 50°C overnight, then brought to room temperature. The crude reaction medium was purified by HPLC. The desired fractions were collected and the organic solvent was evaporated. The

water layer was neutralized with K_2CO_3 and extracted with $MeOH/CH_2Cl_2$ (5/95). The organic layer was dried with $MgSO_4$, filtered and evaporated till dryness. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried under vacuo at $50^\circ C$. Yielding 0.0261g of compound 39.

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b) Preparation of



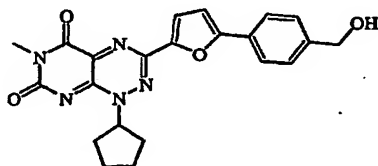
(compound 40)

A mixture of compound 39 (0.0016 mol), HCl (5-6N) in isopropanol (1.5 ml) and isopropanol (15 ml) was heated up to reflux and stirred at $60^\circ C$ for 1 hour, then brought to room temperature. The solvent was removed under reduced pressure. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried under vacuo at $50^\circ C$. Yielding 0.007g of compound 40.

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Example B22

a) Preparation of



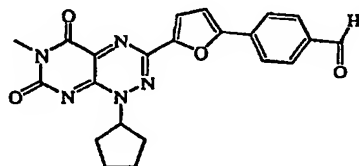
(compound 31)

A solution of 5-phenyl-2-furaldehyde (0.030 mol), THF (250 ml) and Pd/C 10% (2 g) was stirred at room temperature and treated with H_2 for 15 minutes. The a solution of intermediate 62 (0.026 mol), thiophene (2 ml) and $(Et)_3N$ (30 ml) was added drop wise over 2,5 hours. After addition, the reaction mixture was stirred further overnight under H_2 condition. The reaction mixture was filtered over decalite and the filtrate was concentrated under reduced pressure (=fraction 1). The residual fraction (decalite + compound 31) was stirred in DMF at $50^\circ C$, filtered over decalite, washed several times with DMF and concentrated under reduced pressure (=fraction 2). This fraction was stirred in Et_2O and the formed precipitate was filtered off, washed and dried. Yielding 7.3 g of compound 31 (67%).

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b) Preparation of



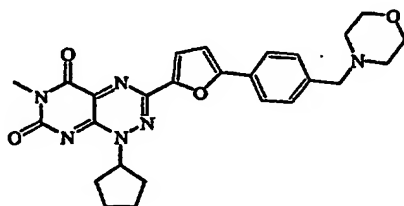
(compound 88)

A mixture of compound 31, MnO_2 (2 g) and CH_2Cl_2 (200 ml) was stirred overnight at room temperature. An extra amount of MnO_2 (12 g) was added and stirred further for 1 day. The reaction was completed and filtered over decalite. The filtrate was concentrated under reduced

25

pressure. The residual fraction was stirred in DIME, filtered, washed and dried under vacuum at 50°C. Yielding: 4g of compound 88 (60%). The product was used as such in the next step.

c) Preparation of



(compound 94)

A mixture of thiophene (1 ml), Pd/C 10% (0,5 g), MeOH (50 ml) and THF (50 ml) was treated with H₂ for 15 minutes. Then compound 88 (0.004 mol) and morpholine (0.011 mol) were added at once and stirred further at room temperature under H₂ conditions for 18 hours. The reaction mixture was filtered over decalite and the filtrate was concentrated. The crude product was purified by HPLC, the desired fractions were collected and concentrated till the organic layer was removed. The water layer was neutralized with K₂CO₃ and the product was extracted with CH₂Cl₂. The organic layer was dried (MgSO₄), filtered and evaporated to dryness. The residual fraction was stirred in DIPE. The precipitate was filtered off and dried under vacuum at 50°C. Yielding: 1,5 g of compound 94 (97%).

Tables 1 & 2 list compounds of the present invention as prepared according to one of the above examples.

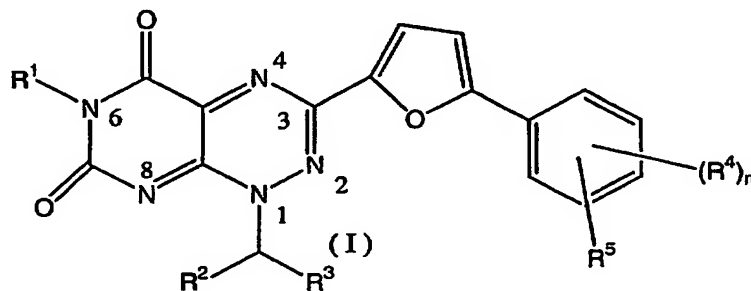
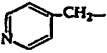
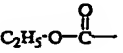
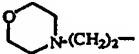
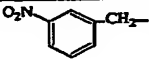
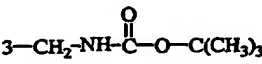
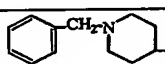
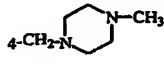
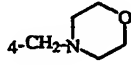
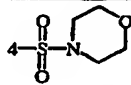
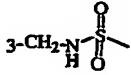
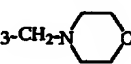
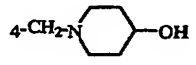
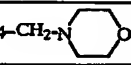
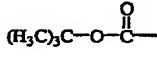
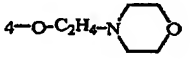
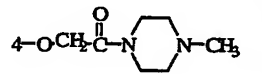
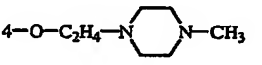
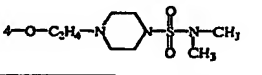
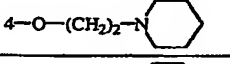
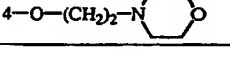
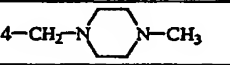
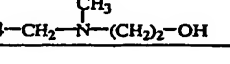
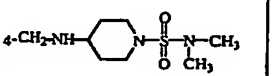


Table 1

Co. No.	R ¹	R ²	R ³	n	R ⁴	R ⁵	Physical data
3	CH ₃	H	H	1	4-Cl	-	
7	CH ₃	H	H	1	3-Cl	-	
41	CH ₃	H	H	1	2-Cl	-	
42	CH ₃	H	H	1	-	2-NO ₂	
43	CH ₃	H	H	1	4-Br	-	
44	CH ₃	H	H	0	-	2-CF ₃	

Co. No.	R ¹	R ²	R ³	n	R ⁴	R ⁵	Physical data
45	CH ₃	H	H	0	-	3-CF ₃	
46	CH ₃	H	H	1	2-Cl	5-CF ₃	
47	CH ₃	H	H	2	2,6 (-Cl) ₂	4-CF ₃	
48	CH ₃	H	H	1	4-Cl	-	
49	CH ₃	H	H	1	3-Cl	-	
50	CH ₃	H	H	1	2-Cl	-	
51	CH ₃	H	H	0	-	2-CF ₃	
52	CH ₃	H	H	0	-	3-CF ₃	
53	CH ₃	H	H	1	2-Cl	5-CF ₃	
54	CH ₃	H	H	0	-	2-NO ₂	
55	CH ₃	H	H	2	2,6 (Cl) ₂	4-CF ₃	
56	CH ₃	H	H	2	2,4 (Cl) ₂	-	
57	CH ₃	H	H	2	2,5 (Cl) ₂	-	
58	CH ₃	H	CH ₃	1	3-Cl	-	
59	CH ₃	H	CH ₃	0	-	2-NO ₂	
60	CH ₃	H	CH ₃	1	2-Cl	-	
61	CH ₃	H	-CH ₂ -OH	1	3-Cl	-	
62		H	H	1	3-Cl	-	
63		H	H	1	3-Cl	-	
64		H	H	1	3-Cl	-	

Co. No.	R ¹	R ²	R ³	n	R ⁴	R ⁵	Physical data
65	H	H	H	1	4-Cl	-	
14	H	H	H	1	3-Cl	-	
66		H	H	1	3-Cl	-	
13	4-C ₂ H ₄ OH	H	H	1	3-Cl	-	
10	CH ₃	H	H	0	-		
11	CH ₃	H	CH ₂ -C ₆ H ₅	1	3-Cl	-	
9	CH ₃	H	H	1	4-CH ₂ -OH	-	
26		H	H	1	3-Cl	-	
67	CH ₃	CH ₃	C ₆ H ₅	1	3-Cl	-	-
8	CH ₃	H	H	0	-		
69	CH ₃	H	H	0	-		
70	CH ₃	CH ₃	(CH ₂) ₂ -CH ₃	1	3-Cl	-	-
71	CH ₃	CH ₃	C ₃ H ₇	1	3-Cl	-	
6	4-CH ₂ -C≡N	H	H	1	3-Cl	-	
72	CH ₃	C ₆ H ₅	C ₆ H ₅	1	3-Cl	-	mp >250°C
73	CH ₃	C ₆ H ₅	C ₆ H ₅	1	3-Cl	-	
74	CH ₃	CH ₃	CH ₃	1	3-Cl	-	mp >260°C
75	CH ₃	CH ₃	CH ₂ -C ₆ H ₅	1	3-Cl	-	mp >250°C
76	CH ₃	CH(CH ₃) ₂	C ₆ H ₅	1	3-Cl	-	mp >250°C

Co. No.	R ¹	R ²	R ³	n	R ⁴	R ⁵	Physical data
5	CH ₃	H	H	1	3-CH ₂ OH	-	
4	CH ₃	H	H	0	-		
2	CH ₃	H	H	0	-		
1	CH ₃	H	H	0	-		
77	CH ₃	H	H	0	-		
23	CH ₃	H	H	0	-	4-formyl	
78	CH ₃	CH ₃	CH ₃	0	-		mp >252°C
17		H	H	1	4-CH ₂ OH	-	
79	CH ₃	H	H	0	-		
80	CH ₃	H	H	0	-		
81	CH ₃	H	H	0	-		
15	CH ₃	H	H	0	-		
82	CH ₃	CH ₃	CH ₃	2	3,5 methoxy		mp 240°C
83	CH ₃	CH ₃	CH ₃	2	3,5 methoxy		mp 247°C
84	CH ₃	CH ₃	CH ₃	0	-	4-CH ₂ -OH	mp>250°C
85	CH ₃	CH ₃	CH ₃	0	-	4-CH ₂ -Cl	-
86	CH ₃	CH ₃	CH ₃	0	-		mp >250°C
87	CH ₃	CH ₃	CH ₃	0	-		mp 229°C
24	CH ₃	H	H	0	-	4-CH=O	
25	CH ₃	CH ₃	CH ₃	0	-		

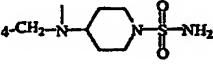
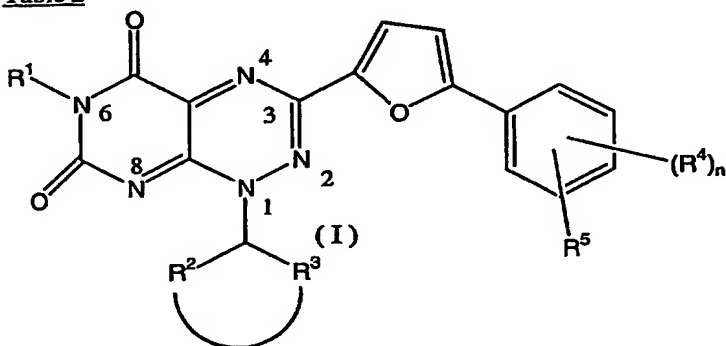

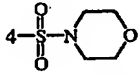
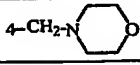
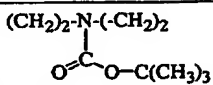
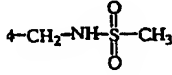
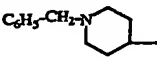
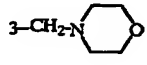
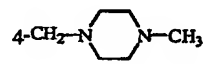
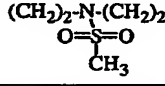
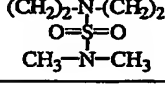
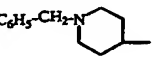
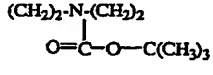
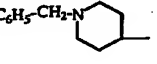
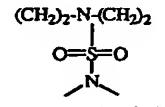
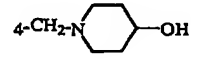
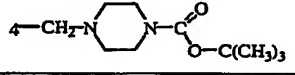
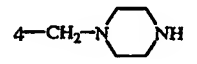
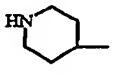
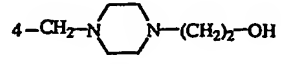
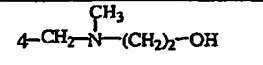
Co. No.	R ¹	R ²	R ³	n	R ⁴	R ⁵	Physical data
68	CH ₃	CH ₃	CH ₃	0	-		

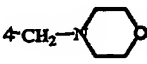
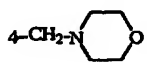
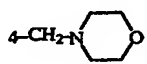
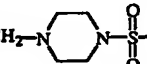

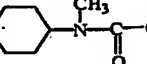
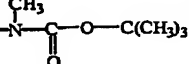
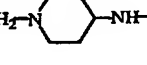
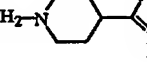



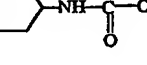
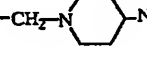
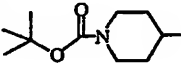
Table 2

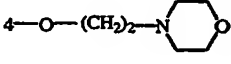
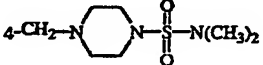
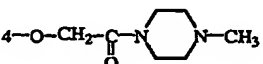
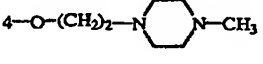
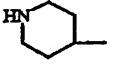
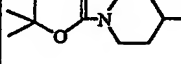
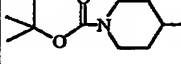
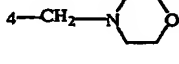
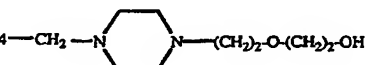
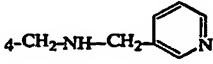
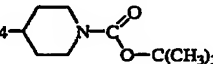
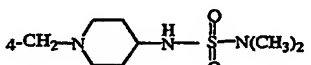
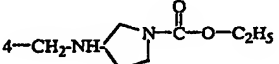
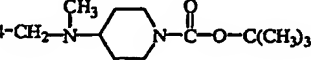
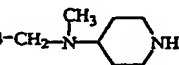


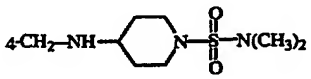
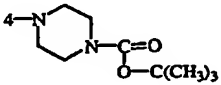
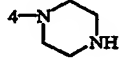
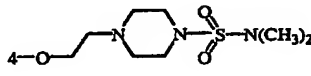

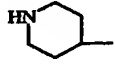


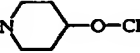
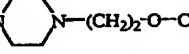

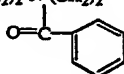

5

Co. No.	R ¹		n	R ⁴	R ⁵	Physical data
89	CH ₃	(CH ₂) ₄	1	3-Cl	-	mp >250°C
90	CH ₃	(CH ₂) ₆	1	3-Cl	-	mp >250°C
91	CH ₃	(CH ₂) ₇	1	3-Cl	-	mp >250°C
92	CH ₃	(CH ₂) ₅	1	3-Cl	-	mp >250°C
93	CH ₃	(CH ₂) ₄	0	-		mp >250°C
94	CH ₃	(CH ₂) ₄	0	-		mp 255°C
95	CH ₃		1	3-Cl	-	mp >250°C
96	CH ₃	(CH ₂) ₂ -NH-(CH ₂) ₂	1	3-Cl	-	mp >250°C
97	CH ₃	(CH ₂) ₄	0	-		mp >250°C

Co. No.	R ¹	$\overset{\text{R}^2}{\text{---}} \overset{\text{R}^3}{\text{---}}$	n	R ⁴	R ⁵	Physical data
27		(CH ₂) ₄	1	3-Cl	-	
98	CH ₃	(CH ₂) ₄	0	-		mp 155°C
31	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ OH	mp 182°C
32	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ Cl	-
99	CH ₃	(CH ₂) ₄	0	-		mp 220°C
100	CH ₃		1	3-Cl	-	mp >250°C
101	CH ₃		1	3-Cl	-	mp >250°C
29			1	3-Cl	-	
30		(CH ₂) ₂ -NH-(CH ₂) ₂	1	3-Cl	-	
102	CH ₃ -		0	-	-	
103	CH ₃	(CH ₂) ₄	0	-		mp >250°C
104	CH ₃	(CH ₂) ₄	0	-		mp 170°C
105	CH ₃	(CH ₂) ₄	0	-		mp >260°C
28		(CH ₂) ₄	0	-	-	
106	CH ₃	(CH ₂) ₄	0	-		mp 175°C
107	CH ₃	(CH ₂) ₄	0	-		mp >250°C

Co. No.	R ¹	$\overset{\text{R}^2}{\text{C}} \text{---} \overset{\text{R}^3}{\text{C}}$	n	R ⁴	R ⁵	Physical data
108	CH ₃	$(\text{CH}_2)_2\text{N}(\text{CH}_2)_2$ $\text{O}=\text{C}-\text{O}-\text{C}(\text{CH}_3)_3$	0	-	4-CH ₂ -N 	-
109	CH ₃	$(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2$	0	-	4-CH ₂ -N 	-
110	CH ₃	$(\text{CH}_2)_2\text{N}(\text{CH}_2)_2$ $\text{O}=\text{S}(=\text{O})\text{CH}_3$	0	-	4-CH ₂ -N 	mp 177°C
111	CH ₃	$(\text{CH}_2)_4$	0	-	3-CH=O	mp 248°C
112	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -N  -N 	mp >250°C
113	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -NH-(CH ₂) ₂ OH	mp 240°C
114	CH ₃	$(\text{CH}_2)_2\text{N}(\text{CH}_2)_2$ $\text{O}=\text{S}(=\text{O})\text{NH}_2$	1	3-Cl	-	mp >250°C
115	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -NH-(CH ₂) ₂ -O-CH ₃	mp 140°C
33	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -N  -N 	-
34	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -N  -NH-CH ₃	-
35	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -N  - 	-
116	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -N  -N 	-
36	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -N  -NH-C(=O)-O-C(CH ₃) ₃	-
37	CH ₃	$(\text{CH}_2)_4$	0	-	4-CH ₂ -N  -NH ₂	-
18		$(\text{CH}_2)_4$	0	-	4-CH ₂ OH	

Co. No.	R ¹	$\overset{\text{R}^2}{\text{---}} \overset{\text{R}^3}{\text{---}}$	n	R ⁴	R ⁵	Physical data
117	CH ₃	(CH ₂) ₄	0	-		mp 173°C
118	CH ₃	(CH ₂) ₄	0	-		mp >250°C
119	CH ₃	(CH ₂) ₄	0	-		mp 252°C
120	CH ₃	(CH ₂) ₄	0	-		mp 196°C
19		(CH ₂) ₄	1	4-Cl	-	-
20		(CH ₂) ₄	1	4-Cl	-	-
21		(CH ₂) ₄	0	-		-
121	CH ₃	(CH ₂) ₄	0	-		mp >250°C
122	CH ₃	(CH ₂) ₄	0	-		mp 205°C
123	CH ₃	(CH ₂) ₄	0	-		mp >250°C
124	CH ₃	(CH ₂) ₄	0	-		-
38	CH ₃	(CH ₂) ₄	0	-		-
39	CH ₃	(CH ₂) ₄	0	-		-
40	CH ₃	(CH ₂) ₄	0	-		-

Co. No.	R ¹	$\overset{\text{R}^2}{\text{C}} \overset{\text{R}^3}{\text{C}}$	n	R ⁴	R ⁵	Physical data
125	CH ₃	(CH ₂) ₄	0	-		-
126	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ -NH-C(CH ₂ OH) ₃	mp 241°C
127	CH ₃	$(\text{CH}_2)_2\text{N}(\text{CH}_2)_2$ HN=C-NH ₂	1	3-Cl	-	mp >260°C
128	CH ₃	(CH ₂) ₄	0	-		mp 240°C
129	CH ₃	(CH ₂) ₄	0	-		mp >250°C
16	CH ₃	(CH ₂) ₂	0	-		
130	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ -N 	mp >260°C
22		(CH ₂) ₄	0	-	4-CH ₂ -N 	
131	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ -N 	mp 218°C
132	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ -N  -O-CH ₃	mp 220°C
133	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ -N  -N(CH ₂) ₂ -O-CH ₃	mp 186°C
134	CH ₃	(CH ₂) ₄	0	-	4-CH ₂ -N(C ₂ H ₄ OH) ₂	mp 242°C
135	CH ₃	(CH ₂) ₄	2	3,5-O- CH ₃	4-O-C ₂ H ₄ -N 	
136	CH ₃	$(\text{CH}_2)_2\text{N}(\text{CH}_2)_2$ 	0	-	4-CH ₂ -N 	

C. Pharmacological examples

Example C.1 : in vitro inhibition of cdk4 using a Scintillant Proximity Assay

The scintillant proximity assay (SPA) is in general described in US patent 4,568,649 (Amersham Pharmacia Biotech). In the present cdk4 SPA kinase reaction assay, a kinase substrate consisting of a fragment of the retinoblastoma protein (pRb) tagged with glutathione-S-transferase (GST), is incubated with the aforementioned protein in the presence of (³³P) radiolabeled ATP. (³³P) phosphorylation of the substrate is subsequently measured as light energy emitted using glutathione-coated SPA beads (Amersham Pharmacia Biotech) by trapping and quantifying the binding of the GST tagged and radiolabeled retinoblastoma protein.

Detailed description

The CDK4 SPA kinase reaction is performed at room temperature for 30 minutes in a 96-well microtiter plate. For each of the tested compounds a full dose response - 10^{-5} M to $3 \cdot 10^{-9}$ M - has been performed. Flavopiridol was used as reference compound. The 100 μ l reaction volume contains 50 mM Hepes, 10 mM NaF, 10 mM MgCl₂, 1 mM Na₃VO₄ pH 7.5, 1.5 μ g CDK4-cell lysate/well, 0.2 μ M unlabeled ATP, 1.7 μ g/well GST-pRb, 1.7 nM AT³³P and 1 μ l of a DMSO solution. The reaction is stopped by diluting the reaction mixture 1/2 with 0.1 mM Na₂EDTA, 0.1 mM non-labeled ATP, 0.05 % Triton-X-100 and 10 mg/ml glutathion coated beads in PBS. The microtiterplates are centrifuges at 900 rpm for 10 minutes and the amount of phosphorylated (³³P) pRb is determined by counting (1 min/well) in a microtiterplate scintillation counter.

Example C.2 : in vitro inhibition of AKT3 using a Scintillant Proximity Assay

The scintillant proximity assay (SPA) is in general described in US patent 4,568,649 (Amersham Pharmacia Biotech). In the present AKT3 SPA kinase reaction assay, a kinase substrate consisting of a fragment of histone H2B tagged with biotine, is incubated with the aforementioned protein in the presence of (³³P) radiolabeled ATP. (³³P) phosphorylation of the substrate is subsequently measured as light energy emitted using streptavidine coated SPA beads (Amersham Pharmacia Biotech) by trapping and quantifying the binding of the biotine tagged and radiolabeled histone H2B fragment.

Detailed description

The AKT3 SPA kinase reaction is performed at 25°C for 3hrs in a 96-well microtiter plate. For each of the tested compounds a full dose response - 10^{-5} M to 3.10^{-9} M – has been performed. Staurosporine was used as reference compound [10^{-7} M to 10^{-9} M]. The assays were performed in the presence of 25mM Hepes, pH 7.0, containing 15 mM $MgCl_2$, 1 mM DTT. Each assay was performed in a 100 μ l reaction volume containing 111nM AKT3 (diluted in 25mM Hepes, pH 7.0, containing 15 mM $MgCl_2$, 1 mM DTT) and the 0.75 μ M Biotinylated Histone H2B and 2nM ATP- P^{33} . The reaction was terminated by addition of 100 μ l Stop mix (50 μ M ATP, 5 mM EDTA, 0.1% BSA, 0.1 % Triton X-100 and 7.5 mg/ml Streptavidin coated PVT SPA beads. After allowing the beads to settle for 30 min, the assay mixture was counted in a microtiterplate scintillation counter.

Example C.3 : in vitro inhibition of AKT3 using a Filter Assay

In the present AKT3 filter assay, a kinase substrate consisting of a fragment of histone H2B, is incubated with the aforementioned protein in the presence of (33 P) radiolabeled ATP. The (33 P)phosphorylated substrate binds to a phosphocellulose cation exchange filter, that can easily be removed from the incubation mixture and counted using a microplate scintillation counter.

Detailed description

AKT3 filter assays were performed at 25°C for 3hrs in the presence of 25mM Hepes, pH 7.0, containing 15 mM $MgCl_2$, 1 mM DTT. Each assay was performed in a 100 μ l reaction volume containing 111nM AKT3 (diluted in 25mM Hepes, pH 7.0, containing 15 mM $MgCl_2$, 1 mM DTT) and the 2.5 μ M Histone H2B and 2nM ATP- P^{32} . The reaction was terminated by addition of 100 μ l 75 mM H_3PO_4 . 90 μ l of the assay mixture was filtered through Phosphocellulose cation exchange paper. After five times washing with 75 μ M H_3PO_4 , the filterpaper was counting in a microtiterplate scintillation counter.

Example C.4 : cellular inhibition of AKT3 using an ELISA

The human breast adenocarcinoma cell line (MDA-MB 231) was used in an phosphospecific antibody cell ELISA (PACE) to assess the inhibitory effect of the compounds on AKT3 mediated phosphorylation of mitogen-activated protein kinase (MAPK). In the experiments the MDA-MB 231 cells were serum starved for 24 hours (5% CO_2 ; 37 °C). Subsequently, the cells are incubated at room temperature for 2 hours with 20 μ M (in serum free medium) of the phosphatidylinositol 3-kinase inhibitor Ly294002 (Alexis, San Diego, CA) prior to the

incubation for 30 minutes with the compounds at a final concentration ranging from 1nM to 3 μ M. After fixation (with 4.5% formaldehyde) for 20 minutes and washing with PBS (0.1M) the cells were successively incubated with for 5 minutes with 0.1% Triton X-100 in PBS, for 20 minutes with 0.6% H_2O_2 and 1 hour with a 2% BSA solution as blocking buffer. After
5 overnight incubation with 0.4 μ g mouse anti-phospho-MAPK E10 (NEB, # 9106) at 4 °C, the phosphorylated MAPK was revealed using 0.5 μ g anti mouse IgG HRP (Promega, # W402B) as secondary antibody followed by a 15 minutes incubation using OPD (Sigma, # 8287) as a detection buffer. The OD (490 – 655 nm) reflected the amount of phosphorylated MAPK and the pIC_{50} of the compounds was based on their effect with respect to blanco (0.1% DMSO) or
10 an internal reference compound treatment.

Example C.5 : in vitro inhibition of CDC25B using the fluorogenic substrate 3-OMFP

CDC25B phosphatase activity is assessed using the fluorogenic substrate 3-O-methyl-fluorescein-phosphate (3-OMFP). The phosphatase-reaction is performed for 1 hour at room
15 temperature in a black microtiter plate in a volume of 50 μ l. The reaction mixture contains 4 μ g/ml CDC25B, 15 μ M (3-OMFP), 15 mM Tris, 50 mM NaCl, 1 mM DTT, 1 mM Na_2EDTA at pH 8.0 and 0.1% DMSO solution at 10^{-5} M and the hits are tested in the same conditions in a full dose/ response from 10^{-5} , 3.10^{-6} , 10^{-6} and 3.10^{-7} M. The enzymatic activity is determined by
20 measuring the fluorescent signal at 485nm (ex.) and 538 (em.).

Example C.6 : cellular inhibition of AKT3 using an ELISA

25 The human breast adenocarcinoma cell line (MDA-MB 231) was used in an phosphospecific antibody cell ELISA (PACE) to assess the inhibitory effect of the compounds on AKT3 mediated phosphorylation of mitogen-activated protein kinase (MAPK). In the experiments the MDA-MB 231 cells were serum starved for 24 hours (5% CO_2 ; 37 °C). Subsequently, the cells are incubated at room temperature for 2 hours with 20 μ M (in serum free medium) of the
30 phosphatidylinositol 3-kinase inhibitor Ly294002 (Alexis, San Diego, CA) prior to the incubation for 30 minutes with the compounds at a final concentration ranging from 1nM to 3 μ M. After fixation (with 4.5% formaldehyde) for 20 minutes and washing with PBS (0.1M) the cells were successively incubated with for 5 minutes with 0.1% Triton X-100 in PBS, for 20 minutes with 0.6% H_2O_2 and 1 hour with a 2% BSA solution as blocking buffer. After
35 overnight incubation with 0.4 μ g mouse anti-phospho-MAPK E10 (NEB, # 9106) at 4 °C, the phosphorylated MAPK was revealed using 0.5 μ g anti mouse IgG HRP (Promega, # W402B) as secondary antibody followed by a 15 minutes incubation using OPD (Sigma, # 8287) as a

detection buffer. The OD (490 – 655 nm) reflected the amount of phosphorylated MAPK and the pIC₅₀ of the compounds was based on their effect with respect to blanco (0.1% DMSO) or an internal reference compound treatment.

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Compound number	CDK4 SPA (Ex. C1) : pIC50 values	AKT3 pep.(Ex. C3) : pIC50 values	AKT cel (Ex. C6) : pIC50 values	Cytotox / survival of A2780 cell after 3 days - pIC50 values	CDC25B WT (Ex. C5) : pIC50 values
67	NT	6.794	6.145	6.708	7.671
93	NT	7.271	6.327	7.277	7.96
94	NT	7.242	7.195	7.276	7.949
96	NT	7.207	8.467	8.000	8.037
2	NT	7.139	6.679	6.310	7.682
1	NT	7.494	7.207	7.208	> 9
98	NT	6.972	6.955	6.971	7.822
31	6.862	7.354	6.558	7.131	7.86
103	NT	7.068	7.184	7.216	7.795
105	NT	6.939	7.008	7.264	7.78
106	NT	7.074	6.99	7.153	7.807
107	NT	7.403	7.019	7.216	7.796
112	6.933	7.196	6.694	6.848	7.704
113	NT	7.488	7.459	7.346	7.847
114	NT	7.345	6.729	6.959	7.819
115	NT	7.318	7.126	7.329	7.878
78	NT	7.237	6.858	7.098	7.946
37	NT	7.286	7.464	7.171	NT
117	6.543	7.306	6.09	6.750	7.723
119	6.888	7.268	6.328	7.318	7.755
121	6.794	7.242	6.391	6.863	7.921
122	7.041	7.51	6.909	7.152	7.853

Compound number	CDK4 SPA (Ex. C1) : pIC50 values	AKT3 pep.(Ex. C3) : pIC50 values	AKT cel (Ex. C6) : pIC50 values	Cytotox / survival of A2780 cell after 3 days - pIC50 values	CDC25B WT (Ex. C5) : pIC50 values
126	7.106	7.096	6.565	5.955	7.028
131	7.285	7.039	7.144	7.210	7.731
87	7.093	7.137	7.454	7.212	7.614
132	7.105	7.328	7.234	7.057	7.695
133	6.949	7.215	7.169	6.924	7.937
134	6.956	7.223	7.407	7.278	7.891
25	7.225	7.19	6.627	7.058	7.731

5 D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable addition salt thereof.

10 Example D.1 : film-coated tablets

Preparation of tablet core

A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinylpyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

20 To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in CH₂Cl₂ (150 ml). Then there were added CH₂Cl₂ (75 ml) and

1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were added magnesium octadecanoate (2.5 g), polyvinyl-pyrrolidone (5 g) and concentrated color suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

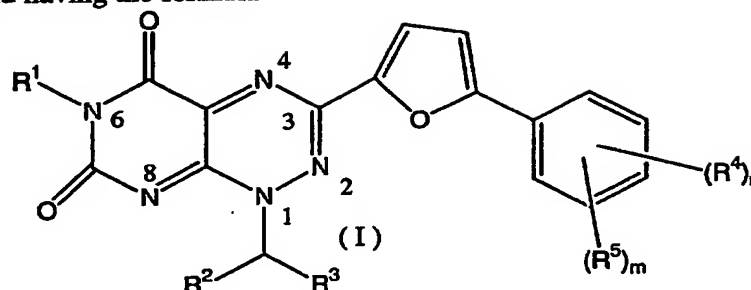
Example D.2 : 2% topical cream

To a solution of hydroxypropyl β -cyclodextrin (200 mg) in purified water is added A.I. (20 mg) while stirring. Hydrochloric acid is added until complete dissolution and next sodium hydroxide is added until pH 6.0. While stirring, glycerol (50 mg) and polysorbate 60 (35 mg) are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of mineral oil (100 mg), stearyl alcohol (20 mg), cetyl alcohol (20 mg), glycerol monostearate (20 mg) and sorbate 60 (15 mg) having a temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

15. 07. 2002

Claims

1. A compound having the formula



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the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein:

m represents an integer being 0 or 1;

10 *n* represents an integer being 0, 1 or 2;

*R*¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with phenyl, pyridinyl or morpholinyl, phenyl, phenyl substituted with one or where possible more substituents being selected from C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, -NO₂ or cyano-C₁₋₄alkyl, piperidinyl or piperidinyl substituted with C₁₋₄alkyl, phenyl-C₁₋₄alkyl or C₁₋₄alkyloxycarbonyl;

*R*² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl or hydroxy;

*R*³ represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl or hydroxy; or

*R*² and *R*³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl or Het¹ wherein said C₃₋₈cycloalkyl or Het¹ each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl

C₁₋₄alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or -C(=NH)-NH₂;

*R*⁴ represents halo, hydroxy or C₁₋₄alkyloxy;

25 *R*⁵ represents formyl, C₁₋₄alkyl, C₁₋₄alkyloxy, Het², -NO₂, -SO₂-Het⁶, aminosulfonyl, -SO₂-NR¹²R¹³,

C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, halo, Het³, NR⁶R⁷ or formyl,

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴, NR⁸R⁹ or -C(=O)-Het⁴;

30

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁵, aminosulphonyl, mono- or di(C₁₋₄alkyl)sulfonyl, C₁₋₄alkylsulfonyl, C₁₋₄alkyloxyC₁₋₄alkyl, methoxyC₁₋₄alkyl or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, Het⁵, C₁₋₄alkyloxycarbonyl or C₁₋₄alkylsulfonyl;

R⁸ and R⁹ are each independently selected from hydrogen, mono- or di(C₁₋₄alkyl)aminosulphonyl or aminosulphonyl;

R¹² and R¹³ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl;

Het¹ represents piperidinyl;

Het² represents a heterocycle selected from piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, aminosulphonyl, mono- or di(C₁₋₄alkyl)aminosulphonyl, NR¹⁰R¹¹, imidazolyl, tetrahydropyrimidinyl, amino, NH₂-SO₂-O-, mono- or di(C₁₋₄alkyl)amino- SO₂-O-, NH₂-SO₂-NH-, mono- or di(C₁₋₄alkyl)amino- SO₂-NH-, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

R¹⁰ and R¹¹ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, or mono- or di(C₁₋₄alkyl)aminosulphonyl;

Het⁴ represents a heterocycle selected from morpholinyl, piperidinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulphonyl, mono- or di(C₁₋₄alkyl)aminosulphonyl or C₁₋₄alkyl substituted with one or more hydroxy;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl, or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulphonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulphonyl;

Het⁶ represents morpholinyl.

2. A compound according to claim 1 wherein;

R¹ represents C₁₋₄alkyl preferably methyl, C₁₋₄alkyl substituted with pyridinyl, phenyl, piperidinyl or piperidinyl substituted with C₁₋₄alkyloxycarbonyl;

R² represents hydrogen or C₁₋₄alkyl preferably methyl;

R³ represents hydrogen or C₁₋₄alkyl preferably methyl; or

R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl or -C(=NH)-NH₂;

R⁴ represents halo or C₁₋₄alkyloxy;

R⁵ represents Het², C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, halo, Het³ or NR⁶R⁷, or R⁵ represents

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het² represents piperazinyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl preferably methyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

3. A compound according to claim 1 wherein;

R¹ represents C₁₋₄alkyl preferably methyl, C₁₋₄alkyl substituted with phenyl, or R¹ represents piperidinyl or piperidinyl substituted with C₁₋₄alkyloxycarbonyl;

R² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl;

R² represents hydrogen, phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with phenyl; or

R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, C₁₋₄alkylsulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or phenylcarbonyl;

R⁴ represents halo, preferably Cl or R⁴ represents C₁₋₄alkyloxy preferably methoxy;

R⁵ represents formyl, C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, Het³ or NR⁶R⁷, or R⁵ represents C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁵, C₁₋₄alkylsulfonyl, methoxyC₁₋₄alkyl, or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

Het² represents piperidinyl optionally substituted with C₁₋₄alkyloxycarbonyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, NR¹⁰R¹¹, imidazolyl, tetrahydropyrimidinyl, amino, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

R¹⁰ and R¹¹ are each independently selected from hydrogen or C₁₋₄alkyl;

Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl;

Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

4. A compound as claimed in any one of claims 1 to 3 wherein R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl, preferably cyclopentyl.

5. A compound as claimed in any one of claims 1 to 4 provided that when R⁵ represents a C₁₋₄alkyloxy substituted with Het⁴, said Het⁴ is being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with one C₁₋₄alkyl, preferably methyl.

6. A compound as claimed in any one of claims 1 to 4 provided that when R^5 represents a C_{1-4} alkyloxy substituted with $-C(=O)-Het^4$, said Het^4 consists of piperazinyl preferably substituted with C_{1-4} alkyl.

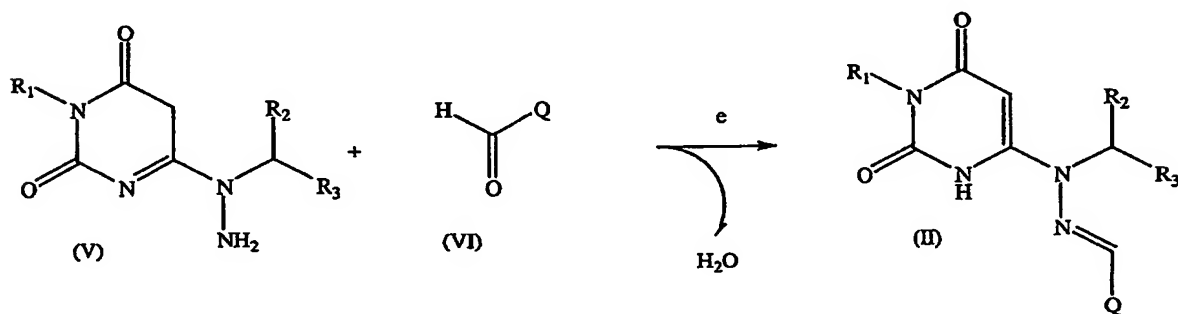
7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in any one of the claims 1 to 6.

8. A process of preparing a pharmaceutical composition as defined in claim 7, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with an effective kinase inhibitory amount of a compound as described in any one of claims 1 to 6.

9. A compound as claimed in any one of claims 1 to 6 for use as a medicine.

10. Use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament for treating cell proliferative disorders such as atherosclerosis, restinosis and cancer.

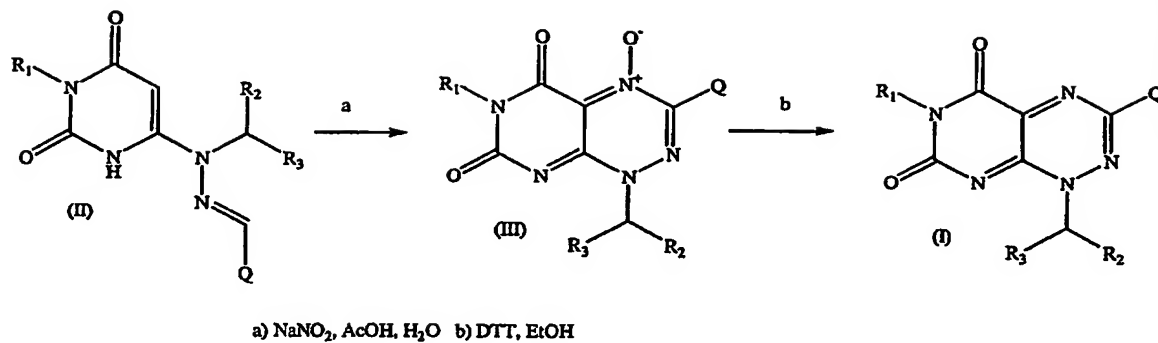
11. A process of preparing a compound as described in claim 1, characterized by i) reacting a primary amine of formula (V) with an aldehyde of formula (VI) in a condensation reaction using ethanol as a suitable solvent;



e) EtOH

ii) followed by a nitrosative cyclisation of the thus obtained Schiff's bases of formula (II) with $NaNO_2$ in acetic acid, and refluxing the nitroso intermediates of formula (III) in a suitable solvent such as acetic anhydride or ethanol further comprising dithiothreitol (DTT);

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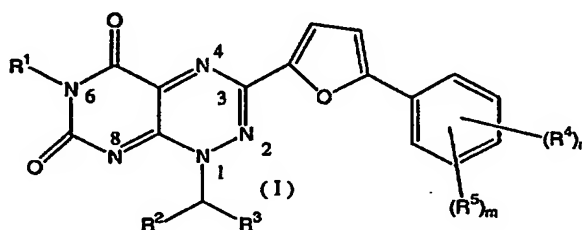


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ABSTRACT3-FURANYL ANALOGS OF TOXOFLAVINE AS KINASE INHIBITORS

The present invention concerns the compounds of formula



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein *m* represents an integer being 0 or 1; *n* represents an integer being 0, 1 or 2; *R*¹ represents C₁₋₄alkyl, C₁₋₄alkyl substituted with pyridinyl, phenyl, piperidinyl or piperidinyl substituted with C₁₋₄alkyloxycarbonyl; *R*² represents hydrogen or C₁₋₄alkyl; *R*³ represents hydrogen or C₁₋₄alkyl; or *R*² and *R*³ taken together with the carbon atom to which they are attached form cyclopentyl or piperidinyl wherein said cyclopentyl or piperidinyl each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, phenylcarbonyl or -C(=NH)-NH₂; *R*⁴ represents halo or C₁₋₄alkyloxy; *R*⁵ represents Het², C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, halo, Het³ or NR⁶R⁷, or C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from Het⁴ or -C(=O)-Het⁴; *R*⁶ and *R*⁷ are each independently selected from hydrogen, C₁₋₄alkyl, Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵; Het² represents piperazinyl; Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl preferably methyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy; Het⁴ represents a heterocycle selected from morpholinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three C₁₋₄alkyl substituents, preferably methyl; Het⁵ represents a heterocycle selected from pyridinyl, pyrrolidinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl.

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